CYCLOBUTYL SUBSTITUTED PYRROLOPYRIDINE AND PYRROLOPYRIMIDINE DERIVATIVES AS JAK INHIBITORS

This application claims the benefit of priority of U.S. Provisional Application No. 61/415,705, filed November 19, 2010, which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

The present invention provides cyclobutyl substituted pyrrolopyrimidines and pyrrolopyridines, as well as their compositions and methods of use, that modulate the activity of Janus kinases (JAKs) and are useful in the treatment of diseases related to the activity of JAKs including, for example, inflammatory disorders, autoimmune disorders, cancer, and other diseases.

BACKGROUND OF THE INVENTION

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.

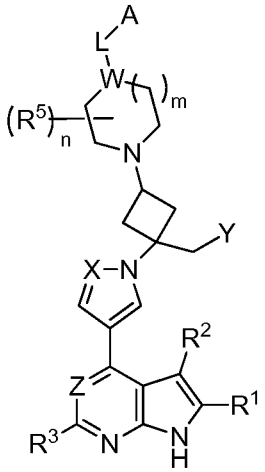
Inhibition of the JAKs may benefit patients suffering from skin immune disorders such as psoriasis, and skin sensitization. The maintenance of psoriasis is believed to depend on a number of inflammatory cytokines in addition to various chemokines and growth factors (JCI, 113:1664-1675), many of which signal through JAKs (*Adv Pharmacol.* 2000;47:113-74).

Accordingly, inhibitors of Janus kinases or related kinases are widely sought. For example, certain JAK inhibitors, including pyrrolopyridine and pyrrolopyrimidines, are reported in U.S. Ser. No. 11/637,545, filed December 12, 2006.

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 OF THE INVENTION

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



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and pharmaceutically acceptable salts thereof; wherein A, L, W, X, Y, Z, R^1, R^2, R^3, R^5, n and m are defined herein.

The present invention further provides pharmaceutical compositions comprising a compound of Formula I as described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

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

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

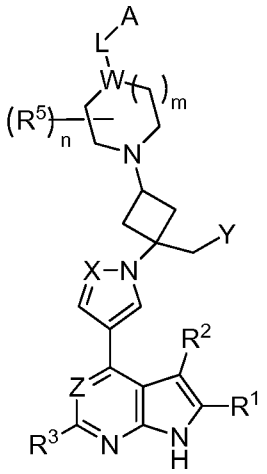
The present invention further provides compounds of Formula I as described herein, or pharmaceutically acceptable salts thereof, for use in methods of modulating a JAK1.

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 treating autoimmune diseases, cancer, myeloproliferative disorders, inflammatory diseases, a bone resorption disease, or organ transplant rejection.

The present invention further 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 a JAK1.

DETAILED DESCRIPTION

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



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or a pharmaceutically acceptable salt thereof; wherein:

X is CH or N;

Y is H, cyano, halo, C_{1-3} alkyl, or C_{1-3} haloalkyl;

Z is CR^4 or N;

W is CH or N;

when W is CH, then L is O, S, $C(R^6)_2$, C(=O), $C(=O)N(R^7)$, C(=O)O, $C(=O)C(R^6)_2$, S(=O), $S(=O)_2$, $S(=O)N(R^7)$, $S(=O)_2N(R^7)$, or $C(=NR^{7a})N(R^7)$; or

when W is N, then L is $C(R^6)_2$, C(=O), C(=O)O, $C(=O)N(R^7)$, $C(=O)C(R^6)_2$, S(=O), $S(=O)_2$, $S(=O)N(R^7)$, $S(=O)_2N(R^7)$, or $C(=NR^{7a})N(R^7)$;

R^1, R^2, R^3, and R^4 are each independently H, hydroxy, halo, C_{1-3} alkyl, or C_{1-3} haloalkyl;

each R^5 is independently hydroxy, C_{1-4} alkoxy, fluorine, C_{1-4} alkyl, hydroxy-C_{1-4}-alkyl, C_{1-4} alkoxy-C_{1-4}-alkyl, or C_{1-4} fluoroalkyl;

each R^6 is, independently, H or C_{1-4} alkyl; or

two R^6 groups, together with the carbon atom to which they are attached, form a 3-, 4-, 5-, or 6-membered cycloalkyl ring;

R^7 is H or C_{1-4} alkyl;

R^{7a} is H, OH, CN, C_{1-4} alkoxy, or C_{1-4} alkyl;

or R^7 and R^{7a}, taken together with the C(=N)N moiety to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl ring or a 5- or 6-membered heteroaryl ring;

A is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocycloalkyl, C_{6-10} aryl, or C_{1-10} heteroaryl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocycloalkyl, C_{6-10} aryl, and C_{1-10} heteroaryl are each optionally substituted with p independently selected R^8 substituents; wherein p is 1, 2, 3, 4, or 5; provided when L is O, S, C(=O), C(=O)O, S(=O), or $S(=O)_2$, then A is not H;

each R^8 is independently selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, C_{1-10} heteroaryl-C_{1-4}-alkyl, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^eR^f$, $-C(=O)R^b$, $-C(=O)OR^a$, $-C(=O)NR^eR^f$, $-OC(=O)R^b$, $-OC(=O)NR^eR^f$, $-NR^eR^f$, $-NR^cC(=O)R^d$, $-NR^cC(=O)OR^d$, $-NR^cC(=O)NR^d$, $-NR^cS(=O)_2R^d$, and $-NR^cS(=O)_2NR^eR^f$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^a, R^c, R^d, R^e, and R^f is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^b is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^g is independently selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, C_{1-7} heteroaryl-C_{1-3}-alkyl, $-OR^{a1}$, $-SR^{a1}$, $-S(=O)R^{b1}$, $-S(=O)_2R^{b1}$, $-S(=O)_2NR^{e1}R^{f1}$, $-C(=O)R^{b1}$, $-C(=O)OR^{a1}$, $-C(=O)NR^{e1}R^{f1}$, $-OC(=O)R^{b1}$, $-OC(=O)NR^{e1}R^{f1}$, $-NR^{e1}R^{f1}$, $-NR^{c1}C(=O)R^{d1}$, $-NR^{c1}C(=O)OR^{d1}$, $-NR^{c1}C(=O)NR^{d1}$, $-NR^{c1}S(=O)_2R^{d1}$, and $-NR^{c1}S(=O)_2NR^{e1}R^{f1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl are each optionally substituted with 1, 2, 3, or 4 independently selected R^h groups;

each R^{a1}, R^{c1}, R^{d1}, R^{e1}, and R^{f1} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^h groups;

each R^{b1} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl,

C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^h groups;

each R^h is independently selected from cyano, halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino, di-C_{1-4}-alkylamino, hydroxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{1-4} alkyl, cyano-C_{1-4} alkyl, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino;

m is 0, 1, or 2; and

n is 0, 1, 2, 3, or 4.

In some embodiments:

X is CH or N;

Y is H, cyano, halo, C_{1-3} alkyl, or C_{1-3} haloalkyl;

Z is CR^4 or N;

W is CH or N;

when W is CH, then L is O, S, $C(R^6)_2$, C(=O), $C(=O)N(R^7)$, C(=O)O, $C(=O)C(R^6)_2$, S(=O), $S(=O)_2$, $S(=O)N(R^7)$, or $S(=O)_2N(R^7)$; or

when W is N, then L is $C(R^6)_2$, C(=O), C(=O)O, $C(=O)N(R^7)$, $C(=O)C(R^6)_2$, S(=O), $S(=O)_2$, $S(=O)N(R^7)$, or $S(=O)_2N(R^7)$;

R^1, R^2, R^3, and R^4 are each independently H, hydroxy, halo, C_{1-3} alkyl, or C_{1-3} haloalkyl;

each R^5 is independently hydroxy, C_{1-4} alkoxy, fluorine, C_{1-4} alkyl, hydroxy-C_{1-4}-alkyl, C_{1-4} alkoxy-C_{1-4}-alkyl, or C_{1-4} fluoroalkyl;

each R^6 is, independently, H or C_{1-4} alkyl; or

two R^6 groups, together with the carbon atom to which they are attached, form a 3-, 4-, 5-, or 6-membered cycloalkyl ring;

R^7 is H or C_{1-4} alkyl;

A is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocycloalkyl, C_{6-10} aryl, or C_{1-10} heteroaryl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocycloalkyl, C_{6-10} aryl, and C_{1-10} heteroaryl are each optionally substituted with p independently selected R^8 substituents; wherein p is 1, 2, 3, 4, or 5;

each R^8 is independently selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, C_{1-10} heteroaryl-C_{1-4}-alkyl, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^eR^f$, $-C(=O)R^b$, $-C(=O)OR^a$, $-C(=O)NR^eR^f$, $-OC(=O)R^b$, $-OC(=O)NR^eR^f$, $-NR^eR^f$, $-NR^cC(=O)R^d$, $-NR^cC(=O)OR^d$, $-NR^cC(=O)NR^d$, $-NR^cS(=O)_2R^d$, and $-NR^cS(=O)_2NR^eR^f$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^a, R^c, R^d, R^e, and R^f is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^b is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^g is independently selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, C_{1-7} heteroaryl-C_{1-3}-alkyl, $-OR^{a1}$, $-SR^{a1}$, $-S(=O)R^{b1}$, $-S(=O)_2R^{b1}$, $-S(=O)_2NR^{e1}R^{f1}$, $-C(=O)R^{b1}$, $-C(=O)OR^{a1}$, $-C(=O)NR^{e1}R^{f1}$, $-OC(=O)R^{b1}$, $-OC(=O)NR^{e1}R^{f1}$, $-NR^{e1}R^{f1}$, $-NR^{c1}C(=O)R^{d1}$, $-NR^{c1}C(=O)OR^{d1}$, $-NR^{c1}C(=O)NR^{d1}$, $-NR^{c1}S(=O)_2R^{d1}$, and $-NR^{c1}S(=O)_2NR^{e1}R^{f1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl are each optionally substituted with 1, 2, 3, or 4 independently selected R^h groups;

each R^{a1}, R^{c1}, R^{d1}, R^{e1}, and R^{f1} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^h groups;

each R^{b1} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^h groups;

each R^h is independently selected from cyano, halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino, di-C_{1-4}-alkylamino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6}

alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino;

m is 0, 1, or 2; and

n is 0, 1, 2, 3, or 4.

In some embodiments, when W is CH, then L is O or S; and when W is N, then L is $C(R^6)_2$, C(=O), C(=O)N(R^7), C(=O)$C(R^6)_2$, S(=O), $S(=O)_2$, S(=O)N(R^7), or $S(=O)_2N(R^7)$.

In some embodiments, X is N.

In some embodiments, Z is N.

In some embodiments, Z is CH.

In some embodiments, W is N.

In some embodiments, L is $C(R^6)_2$, C(=O), C(=O)N(R^7), $S(=O)_2$, or $S(=O)_2N(R^7)$.

In some embodiments, L is $C(R^6)_2$.

In some embodiments, L is C(=O)N(R^7).

In some embodiments, L is $S(=O)_2N(R^7)$.

In some embodiments, L is $C(R^6)_2$, C(=O), C(=O)O, C(=O)N(R^7), $S(=O)_2$, $S(=O)_2N(R^7)$ or $C(=NR^{7a})N(R^7)$.

In some embodiments, L is C(=O)O.

In some embodiments, L is $C(=NR^{7a})N(R^7)$.

In some embodiments, R^6 is H.

In some embodiments, R^7 is H or methyl.

In some embodiments, R^{7a} is CN.

In some embodiments, R^6 is H, R^7 is H or methyl, and R^{7a} is CN.

In some embodiments, L is $S(=O)_2$.

In some embodiments, L is C(=O).

In some embodiments, W is CH.

In some embodiments, L is O.

In some embodiments, Y is cyano.

In some embodiments, R^1, R^2, R^3, and R^4 are each H.

In some embodiments, n is 0, 1, or 2.

In some embodiments, n is 0.

In some embodiments, m is 1.

In some embodiments, A is C_{1-6} alkyl, optionally substituted with p independently selected R^8 substituents.

In some embodiments, A is C_{3-10} cycloalkyl, optionally substituted with p independently selected R^8 substituents.

In some embodiments, A is C_{6-10} aryl, optionally substituted with p independently selected R^8 substituents.

In some embodiments, A is C_{2-10} heterocycloalkyl, optionally substituted with p independently selected R^8 substituents.

In some embodiments, A is C_{1-10} heteroaryl, optionally substituted with p independently selected R^8 substituents.

In some embodiments, A is methyl, ethyl, cyclopropyl, phenyl, a pyrrolidine ring, a piperidine ring, a pyridine ring, a pyrimidine ring, a thiazole ring, or a pyrazine ring; each of which is optionally substituted with p independently selected R^8 substituents.

In some embodiments, A is H, methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, 1,2-dimethylpropyl, 1-(tert-butyl)methyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, a tetrahydropyran ring, a pyrrolidine ring, a piperidine ring, a pyridine ring, a pyrimidine ring, a thiazole ring, or a pyrazine ring; each of which is optionally substituted with p independently selected R^8 substituents; provided when L is O, S, C(=O), C(=O)O, S(=O), or $S(=O)_2$, then A is not H.

In some embodiments, each R^8 is independently selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, C_{1-10} heteroaryl-C_{1-4}-alkyl, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^eR^f$, $-C(=O)R^b$, $-C(=O)OR^a$, $-C(=O)NR^eR^f$, $-OC(=O)R^b$, $-OC(=O)NR^eR^f$, $-NR^eR^f$, $-NR^cC(=O)R^d$, $-NR^cC(=O)OR^d$, $-NR^cC(=O)NR^d$, $-NR^cS(=O)_2R^d$, and $-NR^cS(=O)_2NR^eR^f$; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10}

heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^g groups.

In some embodiments, each R^8 is independently selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^eR^f$, $-C(=O)R^b$, $-C(=O)OR^a$, $-C(=O)NR^eR^f$, $-OC(=O)R^b$, $-OC(=O)NR^eR^f$, $-NR^eR^f$, $-NR^cC(=O)R^d$, $-NR^cC(=O)OR^d$, $-NR^cC(=O)NR^d$, $-NR^cS(=O)_2R^d$, and $-NR^cS(=O)_2NR^eR^f$; wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^g groups.

In some embodiments, each R^8 is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, or $-NR^eR^f$; wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^g groups.

In some embodiments, each R^8 is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{2-7} heterocycloalkyl, $-OR^a$, $-C(=O)OR^a$, or $-NR^eR^f$; wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^g groups.

In some embodiments, each R^8 is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{2-7} heterocycloalkyl, $-OR^a$, $-C(=O)OR^a$, or $-NR^eR^f$; wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^g groups; and wherein each R^a, R^e, and R^f is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl.

In some embodiments, each R^g is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{2-7} heterocycloalkyl, $-OR^{a1}$, $-S(=O)_2R^{b1}$, $-S(=O)_2NR^{e1}R^{f1}$, $-C(=O)R^{b1}$, $-C(=O)OR^{a1}$, $-C(=O)NR^{e1}R^{f1}$, $-OC(=O)R^{b1}$, $-OC(=O)NR^{e1}R^{f1}$, $-NR^{e1}R^{f1}$, $-NR^{c1}C(=O)R^{d1}$, $-NR^{c1}C(=O)OR^{d1}$, $-NR^{c1}C(=O)NR^{d1}$, $-NR^{c1}S(=O)_2R^{d1}$, and $-NR^{c1}S(=O)_2NR^{e1}R^{f1}$; wherein said C_{1-6} alkyl and C_{2-7} heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 independently selected R^h groups.

In some embodiments, each R^g is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{2-7} heterocycloalkyl, $-OR^{a1}$, $-S(=O)_2R^{b1}$, $-S(=O)_2NR^{e1}R^{f1}$, $-C(=O)R^{b1}$, $-C(=O)OR^{a1}$, and $-NR^{e1}R^{f1}$; wherein said C_{1-6} alkyl, C_{3-7}

cycloalkyl, C_{2-7} heterocycloalkyl and are each optionally substituted by 1, 2, 3, or 4 independently selected R^h groups.

In some embodiments, each R^g is independently selected from C_{2-7} heterocycloalkyl and $-NR^{e1}R^{f1}$; wherein said C_{2-7} heterocycloalkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^h groups.

In some embodiments, each R^g is independently selected from C_{2-7} heterocycloalkyl, $-OR^{a1}$, $-NR^{e1}R^{f1}$; wherein said C_{2-7} heterocycloalkyl is optionally substituted by 1 or 2 R^h groups independently selected from fluoro, OH, C_{1-3} alkyl, C_{1-3} alkoxy, and hydroxy-C_{1-4} alkyl; and wherein each R^{a1}, R^{e1} and R^{f1} are independently selected from H, C_{3-7} cycloalkyl, and C_{1-6} alkyl.

In some embodiments, each R^h is independently C_{1-4} alkyl.

In some embodiments, each R^h is independently selected from fluoro, OH, C_{1-3} alkyl, C_{1-3} alkoxy, and hydroxy-C_{1-4} alkyl.

In some embodiments:

each R^a, R^c, R^d, R^e, and R^f is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^b is independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{a1}, R^{c1}, R^{d1}, R^{e1}, and R^{f1} is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^{b1} is independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl.

In some embodiments, p is 1, 2, or 3.

In some embodiments:

X is N;

Z is N;

R^1, R^2, and R^3 are each H;

Y is cyano;

W is N and L is $C(R^6)_2$, C(=O), $C(=O)N(R^7)$, $S(=O)_2$, or $S(=O)_2N(R^7)$; or

W is CH and L is O;

A is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocycloalkyl, C_{6-10} aryl, or C_{1-10} heteroaryl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocycloalkyl, C_{6-10} aryl, and

C_{1-10} heteroaryl are each optionally substituted with p independently selected R^8 substituents; wherein p is 1, 2, 3, 4, or 5;

each R^8 is independently selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^eR^f$, $-C(=O)R^b$, $-C(=O)OR^a$, $-C(=O)NR^eR^f$, $-OC(=O)R^b$, $-OC(=O)NR^eR^f$, $-NR^eR^f$, $-NR^cC(=O)R^d$, $-NR^cC(=O)OR^d$, $-NR^cC(=O)NR^d$, $-NR^cS(=O)_2R^d$, and $-NR^cS(=O)_2NR^eR^f$; wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^g is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{2-7} heterocycloalkyl, $-OR^{a1}$, $-S(=O)_2R^{b1}$, $-S(=O)_2NR^{e1}R^{f1}$, $-C(=O)R^{b1}$, $-C(=O)OR^{a1}$, $-C(=O)NR^{e1}R^{f1}$, $-OC(=O)R^{b1}$, $-OC(=O)NR^{e1}R^{f1}$, $-NR^{e1}R^{f1}$, $-NR^{c1}C(=O)R^{d1}$, $-NR^{c1}C(=O)OR^{d1}$, $-NR^{c1}C(=O)NR^{d1}$, $-NR^{c1}S(=O)_2R^{d1}$, and $-NR^{c1}S(=O)_2NR^{e1}R^{f1}$; wherein said C_{1-6} alkyl and C_{2-7} heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 independently selected R^h groups;

each R^a, R^c, R^d, R^e, and R^f is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^b is independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{a1}, R^{c1}, R^{d1}, R^{e1}, and R^{f1} is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

n is 0; and

m is 1.

In some embodiments:

X is N;

Z is N;

R^1, R^2, and R^3 are each H;

Y is cyano;

W is N and L is $C(R^6)_2$, C(=O), $C(=O)N(R^7)$, $S(=O)_2$, or $S(=O)_2N(R^7)$; or

W is CH and L is O;

A is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocycloalkyl, C_{6-10} aryl, or C_{1-10} heteroaryl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocycloalkyl, C_{6-10} aryl, and

C_{1-10} heteroaryl are each optionally substituted with p independently selected R^8 substituents; wherein p is 1, 2, 3, 4, or 5;

each R^8 is independently selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^eR^f$, $-C(=O)R^b$, $-C(=O)OR^a$, $-C(=O)NR^eR^f$, $-OC(=O)R^b$, $-OC(=O)NR^eR^f$, $-NR^eR^f$, $-NR^cC(=O)R^d$, $-NR^cC(=O)OR^d$, $-NR^cC(=O)NR^d$, $-NR^cS(=O)_2R^d$, and $-NR^cS(=O)_2NR^eR^f$; wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^g is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{2-7} heterocycloalkyl, $-OR^{a1}$, $-S(=O)_2R^{b1}$, $-S(=O)_2NR^{e1}R^{f1}$, $-C(=O)R^{b1}$, $-C(=O)OR^{a1}$, and $-NR^{e1}R^{f1}$; wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-7} heterocycloalkyl and are each optionally substituted by 1, 2, 3, or 4 independently selected R^h groups;

each R^a, R^c, R^d, R^e, and R^f is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^b is independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{a1}, R^{c1}, R^{d1}, R^{e1}, and R^{f1} is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^{b1} is independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

n is 0; and

m is 1.

In some embodiments:

X is N;

Z is N;

R^1, R^2, and R^3 are each H;

Y is cyano;

W is N and L is $C(R^6)_2$, C(=O), $C(=O)N(R^7)$, $S(=O)_2$, or $S(=O)_2N(R^7)$; or

W is CH and L is O;

A is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocycloalkyl, C_{6-10} aryl, or C_{1-10} heteroaryl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocycloalkyl, C_{6-10} aryl, and C_{1-10} heteroaryl are each optionally substituted with p independently selected R^8 substituents; wherein p is 1, 2, 3, 4, or 5;

each R^8 is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, or $-NR^eR^f$; wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^g is independently selected from C_{2-7} heterocycloalkyl and $-NR^{e1}R^{f1}$; wherein said C_{2-7} heterocycloalkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^h groups;

each R^h is independently selected from C_{1-4} alkyl;

each R^a, R^e, and R^f is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^{a1}, R^{e1}, and R^{f1} is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

n is 0; and

m is 1.

In some embodiments:

X is N;

Z is N;

R^1, R^2, and R^3 are each H;

Y is cyano;

W is N and L is $C(R^6)_2$, C(=O), $C(=O)N(R^7)$, $S(=O)_2$, or $S(=O)_2N(R^7)$;

R^6 is H;

R^7 is H or methyl;

A is methyl, ethyl, cyclopropyl, phenyl, a pyrrolidine ring, a piperidine ring, a pyridine ring, a pyrimidine ring, a thiazole ring, or a pyrazine ring; each of which is optionally substituted with p independently selected R^8 substituents; wherein p is 1, 2, or 3;

each R^8 is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, or $-NR^eR^f$; wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^g is independently selected from C_{2-7} heterocycloalkyl and $-NR^{e1}R^{f1}$; wherein said C_{2-7} heterocycloalkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^h groups;

each R^h is independently C_{1-4} alkyl;

each R^a, R^e, and R^f is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^{a1}, R^{e1}, and R^{f1} is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

n is 0; and

m is 1.

In some embodiments:

X is N;

Z is N;

R^1, R^2, and R^3 are each H;

Y is cyano;

W is CH and L is O;

R^6 is H;

R^7 is H or methyl;

A is phenyl, which is optionally substituted with p independently selected R^8 substituents; wherein p is 1, 2, or 3;

each R^8 is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, or $-NR^eR^f$; wherein said C_{1-6} alkyl is optionally substituted by p independently selected R^g groups;

each R^g is independently selected from C_{2-7} heterocycloalkyl and $-NR^{e1}R^{f1}$; wherein said C_{2-7} heterocycloalkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^h groups;

each R^h is independently C_{1-4} alkyl;

each R^a, R^e, and R^f is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^{a1}, R^{e1}, and R^{f1} is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

n is 0; and

m is 1.

In some embodiments:

X is N;

Z is N;

R^1, R^2, and R^3 are each H;

Y is cyano;

W is N and L is $C(R^6)_2$, C(=O), C(=O)O, $C(=O)N(R^7)$, $S(=O)_2$, $S(=O)_2N(R^7)$ or $C(=NR^{7a})N(R^7)$; or

W is CH and L is O;

R^6 is H;

R^7 is H or methyl;

R^{7a} is CN;

A is H, methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, 1,2-dimethylpropyl, 1-(tert-butyl)methyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, a tetrahydropyran ring, a pyrrolidine ring, a piperidine ring, a pyridine ring, a pyrimidine ring, a thiazole ring, or a pyrazine ring; wherein said methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, 1,2-dimethylpropyl, 1-(tert-butyl)methyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, a tetrahydropyran ring, pyrrolidine ring, piperidine ring, pyridine ring, pyrimidine ring, thiazole ring, and pyrazine ring are each optionally substituted with p independently selected R^8 substituents; provided when L is O, S, C(=O), C(=O)O, S(=O), or $S(=O)_2$, then A is not H;

each R^8 is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{2-7} heterocycloalkyl, $-OR^a$, $-C(=O)OR^a$, or $-NR^eR^f$; wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^g groups; and wherein each R^a, R^e, and R^f is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^g is independently selected from C_{2-7} heterocycloalkyl, $-OR^{a1}$, $-NR^{e1}R^{f1}$; wherein said C_{2-7} heterocycloalkyl is optionally substituted by 1 or 2 R^h groups

independently selected from fluoro, OH, C_{1-3} alkyl, C_{1-3} alkoxy, and hydroxy-C_{1-4} alkyl; and wherein each R^{a1}, R^{e1} and R^{f1} are independently selected from H, C_{3-7} cycloalkyl, and C_{1-6} alkyl;

p is 1, 2, or 3;

m is 1; and

n is 0.

In some embodiments:

X is N;

Z is N;

R^1, R^2, and R^3 are each H;

Y is cyano;

W is N and L is $C(R^6)_2$, C(=O), C(=O)O, $C(=O)N(R^7)$, $S(=O)_2$, or $S(=O)_2N(R^7)$; or

W is CH and L is O;

R^6 is H;

R^7 is H or methyl;

A is methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, 1,2-dimethylpropyl, 1-(tert-butyl)methyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, a tetrahydropyran ring, a pyrrolidine ring, a piperidine ring, a pyridine ring, a pyrimidine ring, a thiazole ring, or a pyrazine ring; each of which is optionally substituted with p independently selected R^8 substituents;

each R^8 is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{2-7} heterocycloalkyl, $-OR^a$, $-C(=O)OR^a$, or $-NR^eR^f$; wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^g groups; and wherein each R^a, R^e, and R^f is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

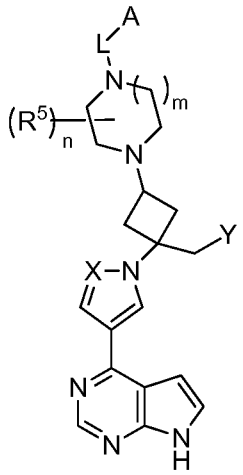
each R^g is independently selected from C_{2-7} heterocycloalkyl, $-OR^{a1}$, $-NR^{e1}R^{f1}$; wherein said C_{2-7} heterocycloalkyl is optionally substituted by 1 or 2 R^h groups independently selected from fluoro, OH, C_{1-3} alkyl, C_{1-3} alkoxy, and hydroxy-C_{1-4} alkyl; and wherein each R^{a1}, R^{e1} and R^{f1} are independently selected from H, C_{3-7} cycloalkyl, and C_{1-6} alkyl;

p is 1, 2, or 3;

m is 1; and

n is 0.

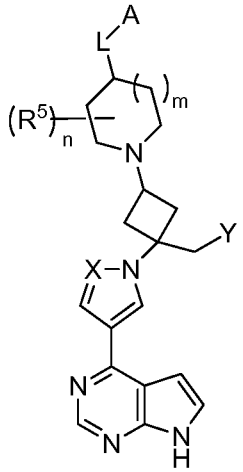
In some embodiments, the compound is a compound of Formula II:



II

or a pharmaceutically acceptable salt thereof.

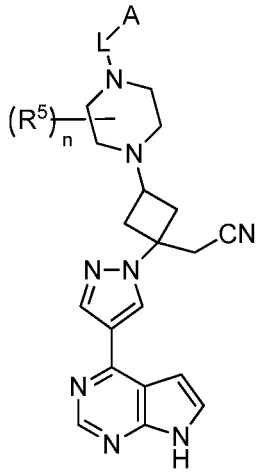
In some embodiments, the compound is a compound of Formula III:



III

or a pharmaceutically acceptable salt thereof.

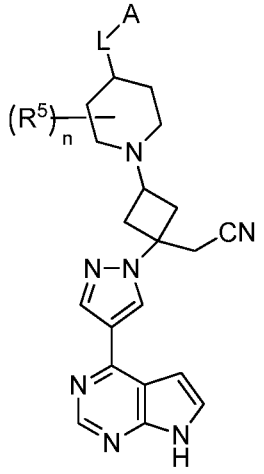
In some embodiments, the compound is a compound of Formula IV:



IV

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is a compound of V:



V

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is a compound selected from:

3-[(4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)methyl]-5-fluorobenzonitrile;

3-[(4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)methyl]-6-(dimethylamino)-2-fluorobenzonitrile;

4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[4-fluoro-2-(trifluoromethyl)phenyl]piperazine-1-carboxamide;

{3-(4-{[(2S)-2-methylpyrrolidin-1-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-(4-{[(2S)-2-ethylpyrrolidin-1-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[3-fluoro-2-(trifluoromethyl)isonicotinoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

[1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile;

{3-[4-(3,5-difluorobenzoyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[(2-chloro-5-fluoropyridin-3-yl)carbonyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[(5-fluoropyridin-3-yl)carbonyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[2-(difluoromethyl)-3-fluoroisonicotinoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

3-[(4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)carbonyl]-5-fluorobenzonitrile;

[1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile;

[1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[6-(trifluoromethyl)pyrazin-2-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile;

{3-[4-(3,4-difluorobenzoyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-[4-(2-chloro-3,6-difluorobenzyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[3-fluoro-5-(trifluoromethyl)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[2-fluoro-4-(trifluoromethyl)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-[4-(pyrrolidin-1-ylcarbonyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)cyclobutyl}acetonitrile;

{3-(4-{[6-(difluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[2-fluoro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[(5-fluoropyridin-3-yl)methyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[(2-isopropylpyrimidin-4-yl)carbonyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-[4-(piperidin-1-ylcarbonyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[4-fluoro-3-(trifluoromethoxy)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-(4-{[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[4-chlorobenzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[2-fluoro-4-(trifluoromethyl)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N,N-dimethylpiperazine-1-carboxamide;

{3-(4-{3-[(dimethylamino)methyl]-5-fluorobenzoyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-(4-{3-[(dimethylamino)methyl]-5-fluorobenzyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-[4-(ethylsulfonyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-[4-(cyclopropylsulfonyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N,N-dimethylpiperazine-1-sulfonamide;

4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-ethyl-N-methylpiperazine-1-carboxamide;

{3-{4-[3-[(dimethylamino)methyl]-5-(trifluoromethyl)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-[4-(3-fluoro-5-{[(2S)-2-methylpyrrolidin-1-yl]methyl}phenoxy)piperidin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-(4-{3-[(dimethylamino)methyl]-5-fluorophenoxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

[cis-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile-d1; and

[trans-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile-d1;

or a pharmaceutically acceptable salt of any of the aforementioned.

In some embodiments, the cyclobutyl ring in Formula I is the *cis* form.

In some embodiments, the cyclobutyl ring in Formula I is the *trans* form.

In some embodiments, if R^5 is hydroxy or C_{1-4} alkoxy and n is not 0, then R^5 is not attached to a carbon adjacent to a nitrogen ring member.

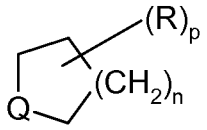
It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

At various places in the present specification, divalent linking substituents are described. It is specifically intended that each divalent linking substituent include both the forward and backward forms of the linking substituent. For example, $-NR(CR'R'')_n-$ includes both $-NR(CR'R'')_n-$ and $-(CR'R'')_nNR-$. Where the structure clearly requires a

linking group, the Markush variables listed for that group are understood to be linking groups.

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 the 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. Throughout the definitions, the term "C_{n-m}" indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. Examples include C_{1-4}, C_{1-6}, and the like.

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 carbons. In some embodiments, the alkyl group contains from 1 to 6 carbon atoms, from 1 to 4 carbon atoms, from 1 to 3 carbon atoms, or 1 to 2 carbon atoms. Examples of alkyl moieties include, but are not limited to, chemical groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, isobutyl, *sec*-butyl; higher homologs such as 2-methyl-1-butyl, *n*-pentyl, 3-pentyl, *n*-hexyl, 1,2,2-trimethylpropyl, and the like.

As used herein, the term "alkylene", employed alone or in combination with other terms, refers to a divalent alkyl linking group. Examples of alkylene groups include, but are not limited to, ethan-1,2-diyl, propan-1,3-diyl, propan-1,2-diyl, butan-1,4-diyl, butan-1,3-diyl, butan-1,2-diyl, 2-methyl-propan-1,3-diyl, and the like.

As used herein, "C_{n-m} alkenyl" refers to an alkyl group having one or more double carbon-carbon bonds and having n to m carbons. In some embodiments, the alkenyl moiety contains 2 to 6 or to 2 to 4 carbon atoms. Example alkenyl groups include, but are not limited to, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl, and the like.

As used herein, "C_{n-m} alkynyl" refers to an alkyl group having one or more triple carbon-carbon bonds and having n to m carbons. Example alkynyl groups include, but are not limited to, ethynyl, propyn-1-yl, propyn-2-yl, and the like. In some embodiments, the alkynyl moiety contains 2 to 6 or 2 to 4 carbon atoms.

As used herein, the term "C_{n-m} alkoxy", employed alone or in combination with other terms, refers to a group of formula -O-alkyl, wherein the alkyl group has n to m carbons. Example alkoxy groups include methoxy, ethoxy, propoxy (e.g., n-propoxy and isopropoxy), t-butoxy, and the like. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "C_{n-m} alkylamino" refers to a group of formula -NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "di-C_{n-m}-alkylamino" refers to a group of formula -$N(alkyl)_2$, wherein the two alkyl groups each has, independently, n to m carbon atoms. In some embodiments, each alkyl group independently has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "C_{n-m} alkoxycarbonyl" refers to a group of formula -C(O)O-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "C_{n-m} alkylcarbonyl" refers to a group of formula -C(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "C_{n-m} alkylcarbonylamino" refers to a group of formula -NHC(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "C_{n-m} alkylsulfonylamino" refers to a group of formula -$NHS(O)_2$-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "aminosulfonyl", employed alone or in combination with other terms, refers to a group of formula -$S(O)_2NH_2$.

As used herein, the term "C_{n-m} alkylaminosulfonyl" refers to a group of formula -$S(O)_2NH(alkyl)$, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "di(C_{n-m} alkyl)aminosulfonyl" refers to a group of formula -$S(O)_2N(alkyl)_2$, wherein each alkyl group independently has n to m carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "aminosulfonylamino" refers to a group of formula -$NHS(O)_2NH_2$.

As used herein, the term "C_{n-m} alkylaminosulfonylamino" refers to a group of formula -$NHS(O)_2NH(alkyl)$, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "di(C_{n-m} alkyl)aminosulfonylamino" refers to a group of formula -$NHS(O)_2N(alkyl)_2$, wherein each alkyl group independently has n to m carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "aminocarbonylamino" refers to a group of formula -$NHC(O)NH_2$.

As used herein, the term "C_{n-m} alkylaminocarbonylamino" refers to a group of formula -NHC(O)NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "di(C_{n-m} alkyl)aminocarbonylamino" refers to a group of formula -$NHC(O)N(alkyl)_2$, wherein each alkyl group independently has n to m carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "C_{n-m} alkylcarbamyl" refers to a group of formula -C(O)-NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "di(C_{n-m}-alkyl)carbamyl" refers to a group of formula –$C(O)N(alkyl)_2$, wherein the two alkyl groups each has, independently, n to m carbon atoms. In some embodiments, each alkyl group independently has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "thio" refers to a group of formula -SH.

As used herein, the term "C_{n-m} alkylthio" refers to a group of formula -S-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "C_{n-m} alkylsulfinyl" refers to a group of formula -S(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "C_{n-m} alkylsulfonyl" refers to a group of formula -$S(O)_2$-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "amino" refers to a group of formula $-NH_2$.

As used herein, the term "hydroxy-C_{n-m}-alkyl" refers to a group of formula -alkylene-OH, wherein said alkylene group has n to m carbon atoms. In some embodiments, the alkylene group has 1 to 4 carbon atoms.

As used herein, the term "C_{o-p} alkoxy-C_{n-m}-alkyl" refers to a group of formula -alkylene-O-alkyl, wherein said alkylene group has n to m carbon atoms and said alkyl group has o to p carbon atoms. In some embodiments, the alkyl and alkylene groups each independently have 1 to 4 carbon atoms.

As used herein, the term "cyano-C_{n-m}-alkyl" refers to a group of formula -alkylene-CN, wherein said alkylene group has n to m carbon atoms. In some embodiments, the alkylene group has 1 to 4 carbon atoms.

As used herein, the term "aryl", employed alone or in combination with other terms, refers to a monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings) aromatic hydrocarbon, such as, but not limited to, phenyl, 1-naphthyl, 2-naphthyl, anthracenyl, phenanthrenyl, and the like. In some embodiments, aryl is C_{6-10} aryl. In some embodiments, the aryl group is a naphthalene ring or phenyl ring. In some embodiments, the aryl group is phenyl.

As used herein, the term "arylalkyl" refers to a group of formula -alkylene–aryl. In some embodiments, arylalkyl is C_{6-10} aryl-C_{1-3} alkyl. In some embodiments, arylalkyl is benzyl.

As used herein, the term "carbamyl" refers to a group of formula $-C(O)NH_2$.

As used herein, the term "carbonyl", employed alone or in combination with other terms, refers to a -C(O)- group.

As used herein, the term "carboxy" refers to a group of formula -C(O)OH.

As used herein, the term "cycloalkyl", employed alone or in combination with other terms, refers to a non-aromatic cyclic hydrocarbon moiety, which may optionally contain one or more alkenylene groups as part of the ring structure. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused rings) ring systems. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo

derivatives of cyclopentane, cyclopentene, cyclohexane, and the like. One or more ring-forming carbon atoms of a cycloalkyl group can be oxidized to form carbonyl linkages. In some embodiments, cycloalkyl is C_{3-12} cycloalkyl, which is monocyclic or bicyclic. Examplary cycloalkyl groups include 1,2,3,4-tetrahydro-naphthalene, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, adamantyl, and the like. In some embodiments, the cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

As used herein, the term "cycloalkylalkyl" refers to a group of formula -alkylene–cycloalkyl. In some embodiments, cycloalkylalkyl is C_{3-12} cycloalkyl-C_{1-3} alkyl, wherein the cycloalkyl portion is monocyclic or bicyclic.

As used herein, "C_{n-m} haloalkoxy" refers to a group of formula –O-haloalkyl having n to m carbon atoms. An example haloalkoxy group is OCF_3. In some embodiments, the haloalkoxy group is fluorinated only. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "C_{n-m} haloalkyl", employed alone or in combination with other terms, refers to an alkyl group having from one halogen atom to 2s+1 halogen atoms which may be the same or different, where "s" is the number of carbon atoms in the alkyl group, wherein the alkyl group has n to m carbon atoms. In some embodiments, the haloalkyl group is fluorinated only. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "C_{n-m} fluoroalkyl" refers to a C_{n-m} haloalkyl wherein the halogen atoms are selected from fluorine. In some embodiments, fluorinated C_{n-m} haloalkyl is fluoromethyl, difluoromethyl, or trifluoromethyl. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms.

As used herein, the term "heteroaryl", employed alone or in combination with other terms, refers to a monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings) aromatic hydrocarbon moiety, having one or more heteroatom ring members selected from nitrogen, sulfur and oxygen. In some embodiments, heteroaryl is 5- to 10-membered C_{1-9} heteroaryl, which is monocyclic or bicyclic and which has 1, 2, 3, or 4

heteroatom ring members independently selected from nitrogen, sulfur and oxygen. When the heteroaryl group contains more than one heteroatom ring member, the heteroatoms may be the same or different. Example heteroaryl groups include, but are not limited to, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, pyrazole, azolyl, oxazole, thiazole, imidazole, furan, thiophene, quinoline, isoquinoline, indole, benzothiophene, benzofuran, benzisoxazole, imidazo[1,2-b]thiazole, purine, or the like.

A five-membered ring heteroaryl is a heteroaryl with a ring having five ring atoms wherein one or more (e.g., 1, 2, or 3) ring atoms are independently selected from N, O, and S. Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl.

A six-membered ring heteroaryl is a heteroaryl with a ring having six ring atoms wherein one or more (e.g., 1, 2, or 3) ring atoms are independently selected from N, O, and S. Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

As used herein, the term "heteroarylalkyl" refers to a group of formula –alkylene-heteroaryl. In some embodiments, heteroarylalkyl is C_{1-9} heteroaryl-C_{1-3} alkyl, wherein the heteroaryl portion is monocyclic or bicyclic and has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen.

As used herein, the term "heterocycloalkyl", employed alone or in combination with other terms, refers to non-aromatic ring system, which may optionally contain one or more alkenylene or alkynylene groups as part of the ring structure, and which has at least one heteroatom ring member independently selected from nitrogen, sulfur and oxygen. When the heterocycloalkyl groups contains more than one heteroatom, the heteroatoms may be the same or different. Heterocycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused rings) ring systems. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the non-aromatic ring, for example, 1,2,3,4-tetrahydro-quinoline and the like. The carbon atoms or heteroatoms in the ring(s) of the

heterocycloalkyl group can be oxidized to form a carbonyl, or sulfonyl group (or other oxidized linkage) or a nitrogen atom can be quaternized. In some embodiments, heterocycloalkyl is 5- to 10-membered C_{2-9} heterocycloalkyl, which is monocyclic or bicyclic and which has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. Examples of heterocycloalkyl groups include 1,2,3,4-tetrahydro-quinoline, azetidine, azepane, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, pyran, and a 2-oxo-1,3-oxazolidine ring.

As used herein, the term "heterocycloalkylalkyl" refers to a group of formula -alkylene-heterocycloalkyl. In some embodiments, heterocycloalkylalkyl is C_{2-9} heterocycloalkyl-C_{1-3} alkyl, wherein the heterocycloalkyl portion is monocyclic or bicyclic and has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen.

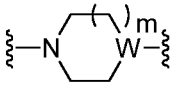
The compounds described herein can be asymmetric (*e.g.*, having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically 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 recrystallization 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

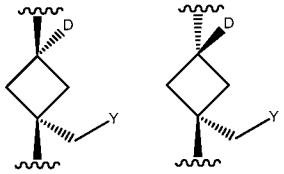
suitable for fractional crystallization methods include stereoisomerically pure forms of α-methylbenzylamine (*e.g.*, *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane, and the like.

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, amide - imidic acid 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 or CH groups in the cyclobutyl 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 moiety  of Formula I are replaced by a CHD, CD_2 or CD group, respectively.

For example, some embodiments of the compounds of Formula I may have a deuterium atom attached to one atom of the cyclobutyl ring:



The term, "compound," as used herein is meant to include all stereoisomers, geometric iosomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified (e.g., in the case of purine rings, unless otherwise indicated, when the compound name or structure has the 9H tautomer, it is understood that the 7H tautomer is also encompassed).

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 conventional 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.

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.

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.

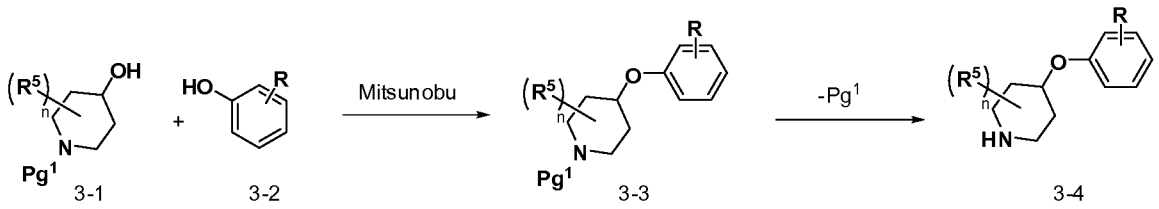
Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and

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).

Useful intermediates **3-4** can be made according to the methods outlined in Scheme 1. The heterocycloalkyl ring compound **3-1** (such as *tert*-butyl 4-hydroxypiperidine-1-carboxylate) can be reacted with phenol **7-2** under Mitsunobu coupling reaction condition to afford ether **3-3**. [*See*, Mitsunobu, O. (**1981**). "The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products ". *Synthesis* **1982** (1): 1-28.] The amino protecting group Pg^1 can be removed to afford intermediate **3-4**.

Scheme 1

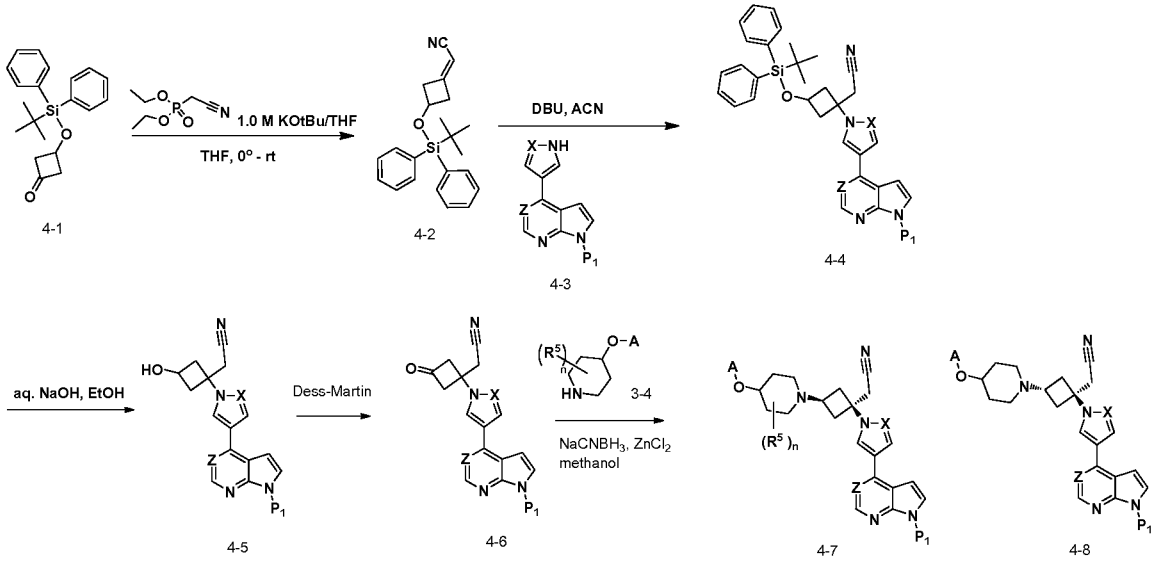


Pg^1 is an amine protecting group such as Boc

Compounds of Formula I, wherein W is CH, can also be made by the methods shown in Scheme 2. Accordingly, compound **4-2** can be formed by reaction of the cyclobutanone **4-1** with a Horner-Wadsworth-Emmons reagent. A protected pyrazol-4-yl-pyrrolo[2,3-d]pyrimidineor pyrrol-3-yl-pyrrolo[2,3-d]pyrimidineof formula **4-3** is

reacted with a protected alkene **4-2** in a Michael addition in the presence of a coupling agent to give compound **4-4**. The ether protecting group can be removed from compound **4-4** to give an alcohol derivative **4-5**, which can be oxidized to give the compound **4-6**. Compound **4-6** can be converted to compound of formula **4-7** and **4-8** via reductive amination, which can be deprotected to remove P_1 to give the compound of Formula I.

Scheme 2

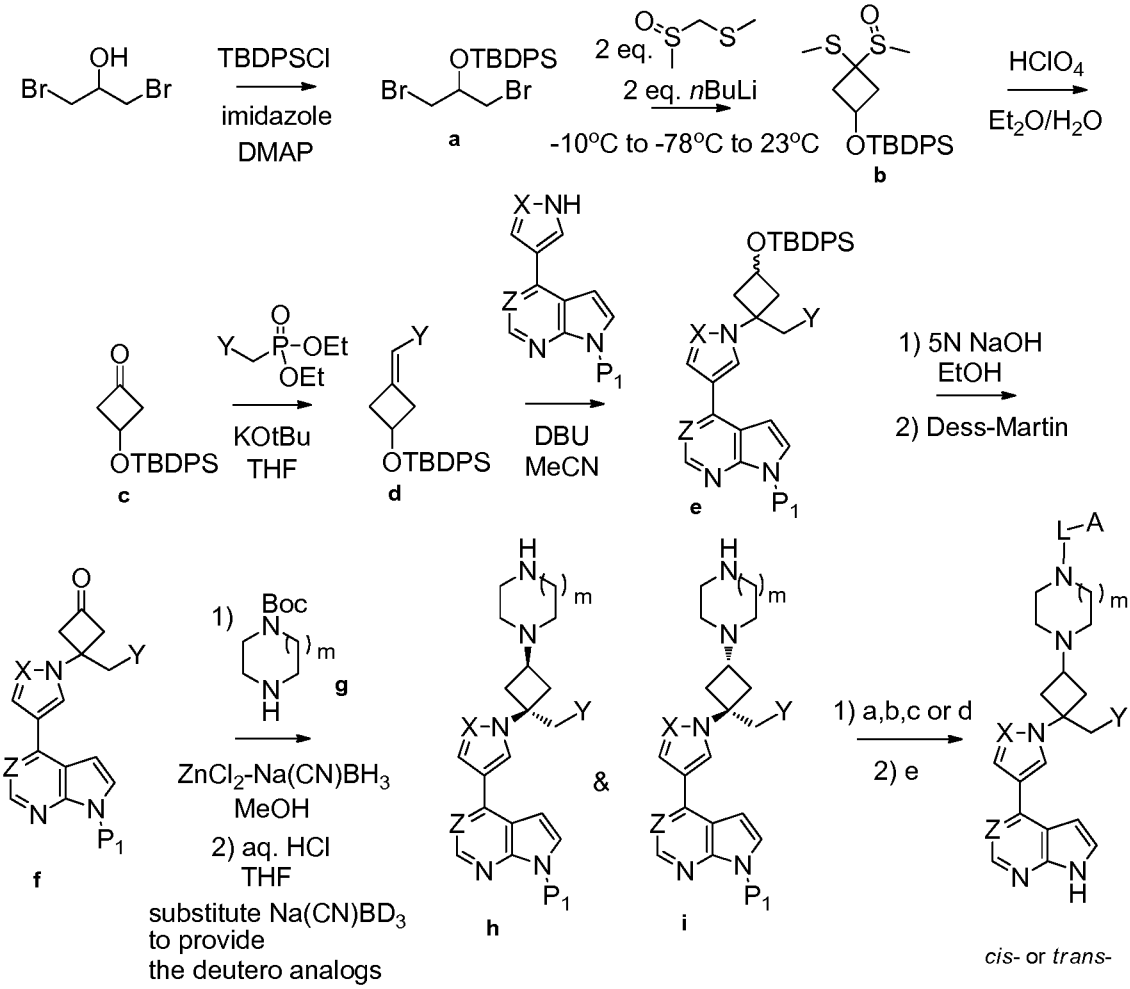


Further compounds of Formula I, wherein W is N, can be prepared as shown in Scheme 3. 1,3-dibromopropan-2-ol can be protected as its tert-butyldiphenylsilyl ether by reaction with tert-butylchlorodiphenylsilane, 1H-imidazole and 4-dimethylaminopyridine in DCM at 0 °C to afford [2-bromo-1-(bromomethyl)ethoxy](tert-butyl)diphenylsilane **a**. By reaction with 2 equivalents of the anion derived from reaction of (methylsulfinyl)(methylthio)methane with n-butyllithium, tert-butyl{[3-(methylsulfinyl)-3-(methylthio)cyclobutyl]oxy}diphenylsilane **b** may be formed. Hydrolysis of this intermediate using perchloric acid in water may afforded 3-{[tert-butyl(diphenyl)silyl]oxy}cyclobutanone **c**. Horner-Wadsworth-Emmons reaction employing the appropriate phosphonate gives the conjugate acceptor **d**. Conjugate addition of 4-(1H-pyrazol-4-yl)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine to this acceptor, mediated by DBU in acetonitrile can provide the TBDPS-

protected alcohol **e**. The silyl protecting group could be removed by action of aqueous NaOH, followed by oxidation of the resulting alcohol to the corresponding ketone **f** by the action of Dess-Martin periodinane. Reductive alkylation of a Boc-protected compound **g** with this ketone, employing a zinc-modified reducing reagent produced by the combination of zinc (II) chloride and sodium cyanoborohydride (*J. Org. Chem.* **1985,** *50*, pp. 1927-1932) can provide the *cis*- and *trans*- isomers **h** and **i** in roughly equal proportions. These may be separated by chiral HPLC into the individual isomers, and the stereochemistry can be determined by nOe. Removal of the Boc protecting group can be effected by stirring with aqueous HCl in THF to afford the base, which can then be functionalized according to the following methods, then deprotected by the use of TFA in DCM followed by ethylenediamine in methanol to afford compounds described herein.

The NH-heterocycle could be reacted with acid chlorides in the presence of base (such as TEA or Hunig's base) to afford amides. Alternatively, amides can be formed by reaction with carboxylic acids using BOP or HATU as coupling agents, in the presence of either of the aforementioned bases. Ureas are formed from the *cis*- or *trans*-cyclobutylpiperazine starting materials either by reaction (in the presence of base) with an isocyanate, or with an intermediate formed by the combination of phosgene with an amine, or with a carbamoyl chloride. Sulfonamides are formed by reaction of the piperazine with sulfonyl chlorides or sulfamoyl chlorides in the presence of base. Alkylated piperazines ($L=CH_2$) were prepared by the combination of an aldehyde, the piperazine, and sodium triacetoxyborohydride in DCM. Where the desired reactants were not commercially available, the preparation used is described in the Examples.

Scheme 3

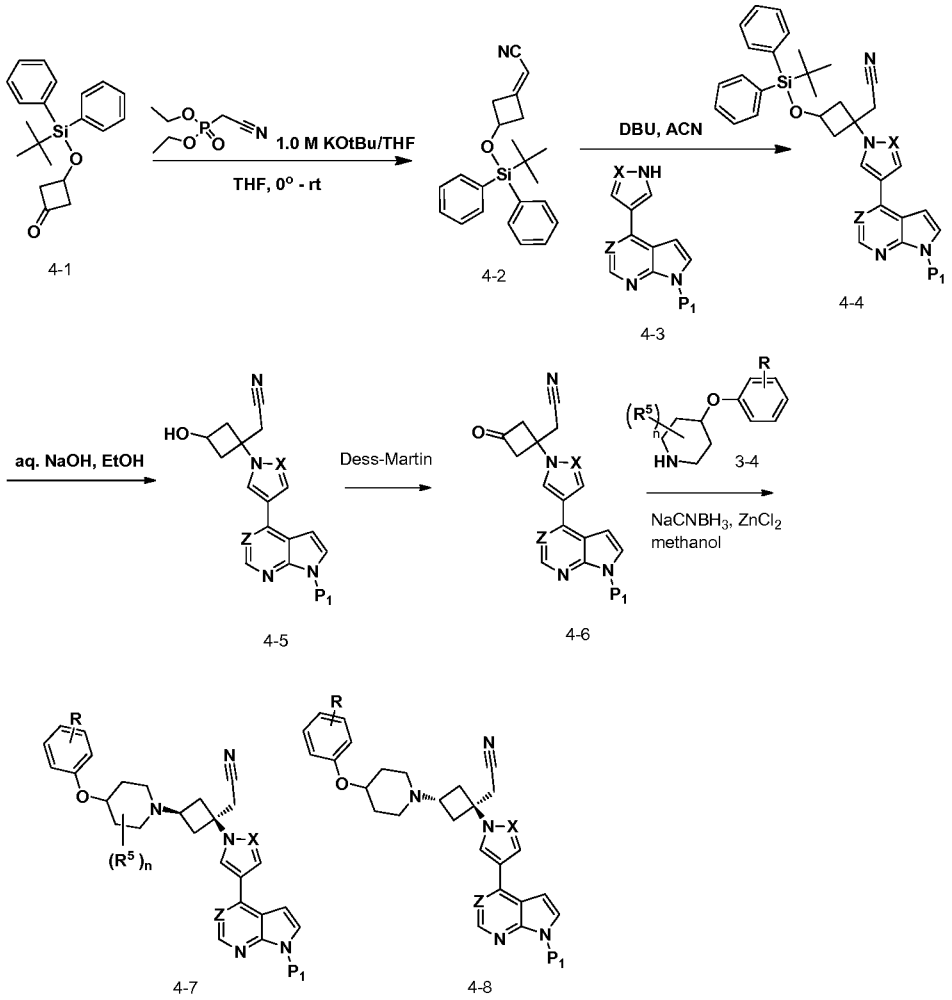


a) L= CO for amides: ACO_2H, BOP or HATU, TEA or DIPEA; or ACOCl, base
b) L= CO for ureas: ANCO, base; or A-H, $COCl_2$, base; or ACOCl, base (e.g. carbamoyl chloride)
c) L= SO_2 for sulfonamides: ASO_2Cl, base (also sulfamoyl chloride)
d) L= CH_2: ACHO, $Na(OAc)BH_3$
e) 1) TFA, DCM 2) ethylenediamine, MeOH

Compound of Formula I can also be made by the methods shown in Scheme IV. Accordingly formula 4-2 can be formed by reaction of the cyclobutanone of formula 4-1 with a Horner-Wadsworth-Emmons reagent. A protected pyrazol-4-yl-pyrrolo[2,3-d]pyrimidine or pyrrol-3-yl-pyrrolo[2,3-d]pyrimidine of formula 4-3 is reacted with a protected alkene of formula 4-2 in a Michael addition in the presence of a coupling agent

to give the compound of formula 4-4. Removal of ether protecting group of formula 4-4 gives an alcohol derivative of formula 4-5, which can be oxidized to give the compound of formula 4-6. The compound of formula 4-6 can be converted to compound of formula 4-7 and 4-8 via reductive amination, which can be deprotected to remove P_1 to give the compound of Formula I.

Scheme 4



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).

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. In some embodiments, the JAK-associated disease is a JAK1-associated disease.

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, 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, atopic dermatitis 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, melanoma etc.), hematological cancers (*e.g.*, lymphoma, leukemia such as acute lymphoblastic leukemia, 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), myelofibrosis with myeloid metaplasia (MMM), 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) or post polycythemia vera/essential thrombocythemia myelofibrosis (Post-PV/ET 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.

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 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 with viral infection, such as influenza and SARS.

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

As used herein, the term "treating" or "treatment" refers to one or more of (1) 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; (2) 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 (3) 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.

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 chemotherapeutic 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), 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, 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(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.

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.

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. 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 an 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 embodiment, 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

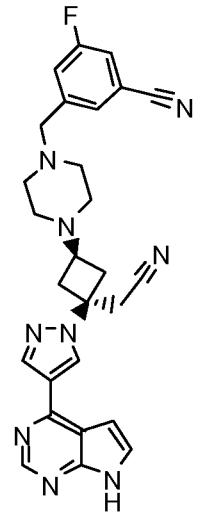
The present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of JAK-associated diseases or disorders, such as cancer, which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound 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.

EXAMPLES

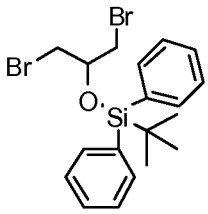
The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the

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 herein. At points throughout the Examples, the stereochemistry of the cyclobutyl ring has been indicated, as currently understood after nOe experiments Boc-protected piperazine intermediates (e.g., products of Example 1a, Step 8).

Example 1a. 3-[(4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)methyl]-5-fluorobenzonitrile



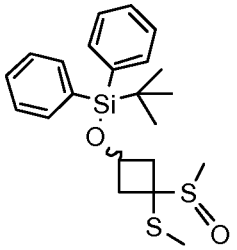
Step 1. [2-bromo-1-(bromomethyl)ethoxy](tert-butyl)diphenylsilane



To a solution of 1,3-dibromo-2-propanol (20.00 g, 91.79 mmol) in methylene chloride (DCM) (100 mL) cooled to 0 °C was added 1H-imidazole (6.56 g, 96.4 mmol) followed by tert-butylchlorodiphenylsilane (25.1 mL, 96.4 mmol) and 4-dimethylaminopyridine (1.12 g, 9.18 mmol). The reaction was stirred with warming to room temperature overnight. The reaction mixture was diluted with diethyl ether, washed

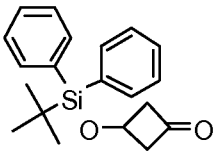
with water, and the aqueous layer was again extracted once with ether. The combined organic extracts were washed with water, followed by brine, dried over sodium sulfate, decanted and concentrated. Flash chromatography (eluting with a gradient from 0-15% ethyl acetate/hexanes) afforded desired product (42 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72-7.66 (m, 4H), 7.51-7.37 (m, 6H), 4.00-3.91 (m, 1H), 3.49-3.45 (m, 4H), 1.09 (s, 9H).

Step 2. tert-butyl{[3-(methylsulfinyl)-3-(methylthio)cyclobutyl]oxy}diphenylsilane



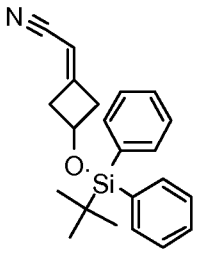
To a solution of (methylsulfinyl)(methylthio)methane (27.70 g, 223.0 mmol) in tetrahydrofuran (90 mL) at -10 °C was added dropwise, a solution of 2.5 M n-butyllithium in hexane (89.2 mL, 223 mmol). The mixture was stirred at -10 °C for 2 hours. It was then cooled to -78 °C and transferred by cannula in a slow manner to a solution of [2-bromo-1-(bromomethyl)ethoxy](tert-butyl)diphenylsilane (42 g, 93 mmol, from Step 1) in tetrahydrofuran (70 mL, 900 mmol) held at -78 °C. The mixture was stirred with warming to room temperature over 2 nights. Water was added, and then the product was extracted with three portions of DCM. The combined extracts were dried over sodium sulfate, filtered and concentrated. Flash chromatography (eluting with a gradient from 0-100% ethyl acetate/hexanes) afforded desired product as a mixture of diastereomers (34.1 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$), diastereomers: δ 7.74-7.58 (m, 8H), 7.48-7.31 (m, 10H), 4.52 (tt, 1H), 4.42 (tt, 1H), 3.05-1.99 (m, 8H), 2.47 (s, 3H), 2.42 (s, 3H), 2.13 (s, 3H), 2.00 (s, 3H), 1.05 (s, 9H), 1.02 (s, 9H).

Step 3. 3-{[tert-butyl(diphenyl)silyl]oxy}cyclobutanone



A solution of tert-butyl{[3-(methylsulfinyl)-3-(methylthio)cyclobutyl]oxy}diphenylsilane (17.05 g, 40.7 mmol, from Step 2) in ether (350 mL) cooled to 0 °C was treated with a solution of 6 M perchloric acid in water (10 mL) that was pre-diluted with water (7 mL). The bath was removed and stirred overnight. The mixture was poured into pH 7 buffer, and the product was extracted with diethyl ether. The combined extracts were dried over sodium sulfate, decanted and concentrated. The reaction was performed again on the same scale and the two batches were combined for purification. Flash chromatography, eluting with a gradient from 0-5% ethyl acetate/hexanes afforded desired product (15.7 g, 59%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75-7.62 (m, 4H), 7.49-7.33 (m, 6H), 4.59 (tt, 1H), 3.22-3.03 (m, 4H), 1.07 (s, 9H).

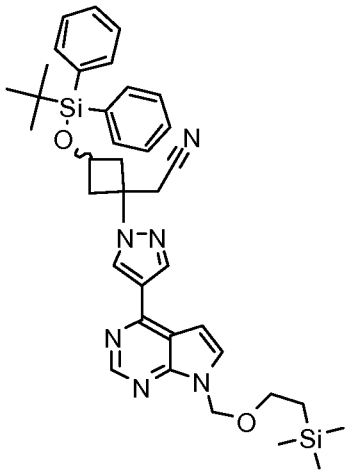
Step 4. (3-{[tert-butyl(diphenyl)silyl]oxy}cyclobutylidene)acetonitrile



To a solution of 1.0 M potassium *tert*-butoxide in tetrahydrofuran (46.0 mL, 46.0 mmol) at 0 °C was added diethyl cyanomethylphosphonate (7.8 mL, 48 mmol). The bath was removed and the reaction mixture was allowed to warm to room temperature over 1 hour. The reacation was re-cooled to 0 °C, and a solution of 3-{[tert-butyl(diphenyl)silyl]oxy}cyclobutanone (15.7 g, 48.4 mmol, from Step 3) in tetrahydrofuran (80 mL) was added. During the course of the addition, additional tetrahydrofuran (50 mL) was added into the receiving flask to facilitate stirring. Upon complete addition of the ketone, the bath was removed and the reaction allowed to reach room temperature and stirred overnight. The reaction mixture was partitioned between

water and ethyl acetate and the aqueous was extracted with ethyl acetate a total of three times. The combined extracts were washed with brine, dried over sodium sulfate, decanted and concentrated. Flash chromatography, eluting with a gradient of 0-10% ethyl acetate in hexanes afforded product (16.1 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74-7.58 (m, 4H), 7.49-7.34 (m, 6H), 5.13 (dddd, 1H), 4.34 (tt, 1H), 3.16-2.90 (m, 4H), 1.05 (s, 9H).

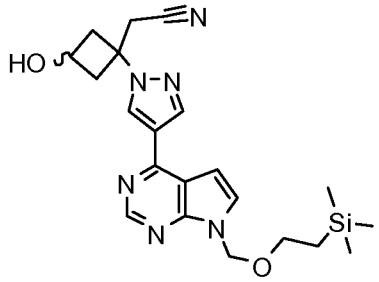
Step 5. cis and trans {3-{[tert-butyl(diphenyl)silyl]oxy}-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



To a solution of (3-{[tert-butyl(diphenyl)silyl]oxy}cyclobutylidene)acetonitrile (16.1 g, 35.2 mmol, from Step 4) and 4-(1H-pyrazol-4-yl)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine (11.1 g, 35.2 mmol) (prepared as in WO2007/070514 Example 65, Step 2) in acetonitrile (100 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (5.3 mL, 35 mmol). The reaction was stirred over three nights. The acetonitrile was removed *in vacuo*. Flash chromatography, eluting with 25% ethyl acetate in hexanes until product began to elute, then 40 to 66% ethyl acetate in hexanes was used to elute desired product as a mixture of diastereomers (17.4 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$), diastereomers (M=major, min=minor): δ 8.86 (s, 1H M), 8.81 (s, 1H min), 8.37 (s 1H, M), 8.30 (s, 1H M), 8.26 (s, 1H min), 8.25 (s, 1H min), 7.67-7.35 (m, 11H M & 11H min), 6.81 (d, 1H M), 6.73 (d, 1H min), 5.68 (s, 2H M),

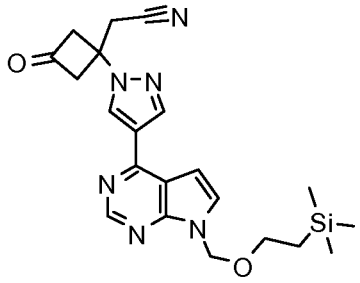
5.66 (s, 2H min), 4.45 (tt, 1H min), 4.33 (tt, 1H M), 3.59-3.50 (m, 2H M & 2H min), 3.23 (s, 2H min), 3.11-3.00 (m, 2H min), 2.90 (s, 2H M), 2.88-2.80 (m, 4H M), 2.64-2.54 (m, 2H min), 1.08 (s, 9H min), 1.03 (s, 9H M), 0.97-0.88 (m, 2H M & 2H min), -0.06 (s, 9H M), -0.07 (s, 9H min); LCMS $(M+H)^+$: 663.3.

Step 6. cis and trans {3-hydroxy-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



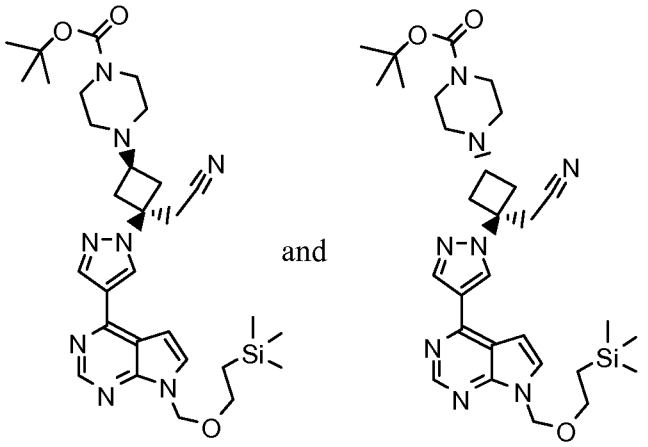
To {3-{[tert-butyl(diphenyl)silyl]oxy}-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (8.7 g, 13.1 mmol, as a mixture of diastereomers from Step 5) in ethanol (355 mL) was added 5.0 M sodium hydroxide in water (90 mL, 450 mmol). The reaction was stirred for 5 hours. Additional water was added and then the ethanol was removed using rotary evaporation. The mixture was then partitioned between ethyl acetate and water. The aqueous portion was extracted with ethyl acetate a total of three times. The combined organic extracts were washed with water, then brine, dried over sodium sulfate, decanted and concentrated. The residue was azeotroped with benzene. This reaction was performed again on the same scale and the crude product of both runs was combined for purification. Flash chromatography, eluting with a gradient from 0-10% MeOH in DCM afforded product as an off-white foam (9.3 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$), diastereomers (M=major, min=minor): δ 8.84 (s, 1H M & 1H min), 8.41 (s, 1H min), 8.39 (s, 1H M), 8.31 (s, 1H min), 8.30 (s, 1H M), 7.40 (d, 1H M & 1H min), 6.80 (d, 1H M & 1H min), 5.67 (s, 2H M & 2H min), 4.60-4.44 (m, 1H M & 1H min), 3.59-3.46 (m, 2H M & 2H min), 3.25 (s, 2H min), 3.25-3.16 (m, 2H min), 3.08 (s, 2H M), 3.10-3.00 (m, 2H M), 2.84-2.73 (m, 2H M), 2.64-2.51 (m, 2H min), 0.97-0.87 (m, 2H M & 2H min), -0.06 (s, 9H M & 9H min); LCMS $(M+H)^+$: 425.0.

Step 7. {3-oxo-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



To a solution of {3-hydroxy-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (9.3 g, 22 mmol, as a mixture of diastereomers from Step 6) in methylene chloride (300 mL) at 0 °C was added Dess-Martin periodinane (10.0 g, 24 mmol). After a reaction time of 2 hours, the mixture was poured into 1N NaOH and extracted with three portions of DCM. The combined extracts were washed with further 1N NaOH, dried over sodium sulfate, decanted and the solvent removed *in vacuo*. Flash chromatography, eluting with a gradient from 0-10% MeOH in DCM afforded product as a yellow foam. Theoretical yield assumed for use in Step 8. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.50 (s, 1H), 8.35 (s, 1H), 7.42 (d, 1H), 6.80 (d, 1H), 5.68 (s, 2H), 4.11-4.00 (m, 2H), 3.74-3.61 (m, 2H), 3.59-3.50 (m, 2H), 3.31 (s, 2H), 0.96-0.88 (m, 2H), -0.06 (s, 9H); LCMS $(M+H)^+$: 423.0.

Step 8. tert-butyl 4-{cis-3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazine-1-carboxylate; and tert-butyl 4-{trans-3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazine-1-carboxylate



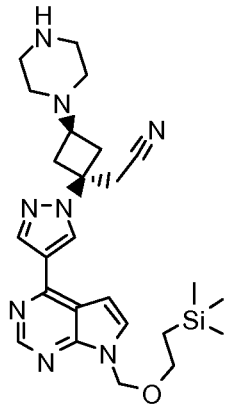
Sodium cyanoborohydride (0.693 g, 11.0 mmol) and zinc dichloride (0.752 g, 5.51 mmol) were precombined in methanol and stirred for 2 hours as described in *J. Org. Chem.* **1985,** *50*, pp. 1927-1932. {3-Oxo-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (4.66 g, 11.0 mmol, from Step 7) and tert-butyl piperazine-1-carboxylate (4.11 g, 22.0 mmol) were dissolved in methanol (200 mL), then the pre-mixed solution of sodium cyanoborohydride and zinc dichloride was added. The reaction was left to stir over 4 nights. The methanol was removed *in vacuo*. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The aqueous layer was extracted with two further portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and concentrated. Flash chromatograpy, eluting with a gradient from 0-10% MeOH in DCM afforded the product as a mixture of diastereomers. Chiral HPLC (Chiralcel OJ-H, 20 x 250 mm, 5 u packing, 30% EtOH/70% Hexanes at a flow rate of 12 mL/min, with a loading of about 31 mg/injection) was used to separate the *cis* and *trans* diastereomers. Peak 1, *cis*: (retention time 9.80 min): 1.48 g, 23%; and Peak 2, *trans*: (retention time 13.54 min): 1.58 g, 24%.

^{1}H NMR peak 1 (300 MHz, CD_3OD): δ 8.70 (s, 1H), 8.63 (s, 1H), 8.35 (s, 1h), 7.58 (d, 1H), 7.01 (d, 1H), 5.65 (s, 2H), 3.60-3.52 (m, 2H), 3.46-3.38 (m, 4H), 2.92 (tt, 1H), 2.83-2.72)m, 2H), 2.72-2.60 (m, 2H), 2.40-2.29 (m, 4H), 1.44 (s, 9H), 0.90-0.82 (m, 2H), -0.10 (s, 9H); LCMS $(M+H)^+$: 593.4.

^{1}H NMR peak 2 (400 MHz, d_6-dmso): δ 8.72 (s, 1H), 8.71 (s, 1H), 8.39 (s, 1H), 7.61 (d, 1H), 7.04 (d, 1H), 5.67 (s, 2H), 3.62-3.53 (m, 2H), 3.50-3.40 (m, 4H), 3.32 (dd,

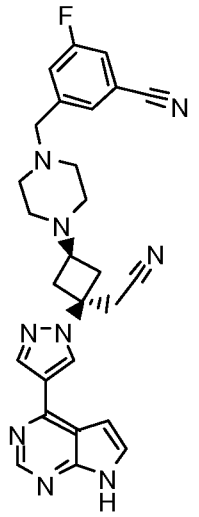
2H), 3.11-3.01 (m, 2H), 2.89 (tt, 1H), 2.53-2.42 (m, 2H), 2.40-2.31 (m, 4H), 1.44 (s, 9H), 0.92-0.82 (m, 2H), -0.09 (s, 9H); LCMS $(M+H)^+$: 593.4.

Step 9. {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



To a solution of tert-butyl 4-{cis-3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazine-1-carboxylate (1.48 g, 2.50 mmol, Peak 1 from Step 8) in 1,4-dioxane (90 mL) was added 4.0 M HCl in water (20 mL, 60 mmol) and was stirred over two nights. The reaction mixture was poured into saturated sodium bicarbonate, sufficient quantity to become basic. Dioxane was removed *in vacuo*. The product was extracted with three portions of ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, decanted and concentrated. The product was used without further purification (1.18 g, 96%). LCMS $(M+H)^+$: 493.1.

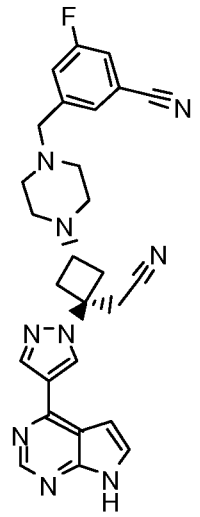
Step 10. 3-[(4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)methyl]-5-fluorobenzonitrile



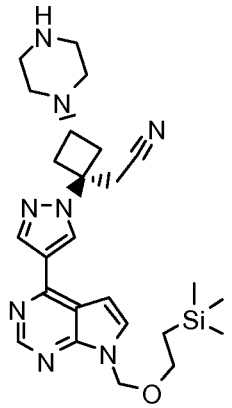
{cis-3-Piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.080 g, 0.16 mmol, from Step 9) and 3-bromo-5-fluorobenzaldehyde (0.046 g, 0.23 mmol, Matrix Scientific) were combined in methylene chloride (3 mL) and after 10 minutes, sodium triacetoxyborohydride (0.138 g, 0.649 mmol) was added. The reaction was continued overnight. 1N NaOH was added into the mixture, and then the product was extracted with three portions of ethyl acetate. The combined extracts were dried over sodium sulfate, decanted and concentrated. The crude product was then dissolved in N,N-dimethylformamide (2 mL) , and zinc cyanide (0.114 g, 0.974 mmol) was added. The mixture was degassed by bubbling a stream of nitrogen through the mixture for 10 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.04 g, 0.03 mmol) was added, the reaction vessel was sealed and heated in the microwave to 120 °C for 30 minutes. The mixture was partitioned between water and ethyl acetate. The aqueous was extracted with ethyl acetate a total of three times. The combined extracts were washed with water, then brine, dried over sodium sulfate, decanted and concentrated. The crude product was stirred in a 1:1 mix of TFA:DCM (4 mL) for 2 hours. The solvents were evaporated, and the residue was stirred with 0.3 mL ethylenediamine in methanol (4 mL) overnight. The mixture was filtered and purified by preparative HPLC-MS (C18 eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford desired product as the free base (0.01 g, 10%). ^1H NMR

(300 MHz, CD_3OD): δ 8.66 (s, 1H), 8.65 (s, 1H), 8.37 (s, 1H), 7.57 (dd, 1H), 7.51 (d, 1H), 7.50-7.43 (m, 2H), 6.98 (d, 1H), 3.62 (s, 2H), 3.35 (s, 2H), 3.13-2.99 (m, 1H), 2.88-2.77 (m, 2H), 2.77-2.66 (m, 2H), 2.65-2.40 (br, 8H); ^{19}F NMR (376 MHz, d_6-dmso): δ -111.45 (dd, 1F); LCMS $(M+H)^+$: 496.3.

Example 1b. 3-[(4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)methyl]-5-fluorobenzonitrile



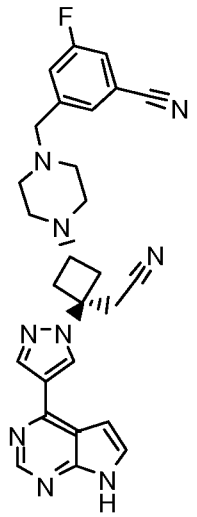
Step 1. {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



To a solution of tert-butyl 4-{trans-3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazine-1-carboxylate (1.58 g, 2.66 mmol, Peak 2 from Example 1a, Step 8) in 1,4-dioxane (100 mL) was added 4.0 M hydrogen chloride in water (20 mL)

and stirred overnight for two nights. The reaction mixture was poured into saturated sodium bicarbonate in sufficient quantity to neutralize and become basic. Dioxane was then removed from the mixture *in vacuo*. The product was extracted with three portions of ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, decanted and concentrated. The product was used without further purification (1.3 g, 100%). LCMS $(M+H)^+$: 493.1.

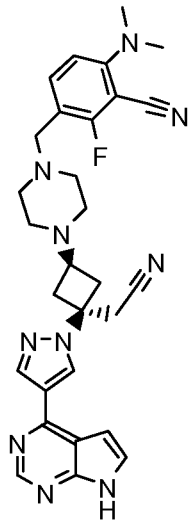
Step 2. 3-[(4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)methyl]-5-fluorobenzonitrile



{trans-3-Piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.047 g, 0.095 mmol, from Step 1) and 3-bromo-5-fluorobenzaldehyde (0.027 g, 0.13 mmol, Matrix Scientific) were stirred in methylene chloride (1 mL) for 10 minutes, then sodium triacetoxyborohydride (0.0809 g, 0.382 mmol) was added. The reaction was continued overnight. 1N NaOH was added, and then the product was extracted with three portions of ethyl acetate. The combined extracts were dried over sodium sulfate, decanted and concentrated. The crude product was dissolved in N,N-dimethylformamide (2 mL), zinc cyanide (0.12 g, 1.0 mmol) was added, then the mixture was degassed by passing a stream of nitrogen through for 10 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.040 g, 0.035 mmol) was added. The reaction vessel was sealed and heated in the

microwave for 30 minutes at 120 °C. The reaction mixture was partitioned between water and ethyl acetate. The product was extracted with a total of three portions of ethyl acetate. The combined extracts were washed with water, then brine, dried over sodium sulfate, decanted and concentrated. The residue was stirred in a 1:1 mix of trifluoroacetic (TFA):DCM (4 mL) for 2 hours, and the solvents were removed *in vacuo*. The residue was then stirred with 0.3 mL ethylenediamine in 4 mL methanol overnight. The reaction mixture was filtered and purified by preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing desired mass was frozen and lyophilized to afford product as the free base (0.01 g, 10%). ^{1}H NMR (300 MHz, CD_3OD): δ 8.72 (s, 1H), 8.67 (s, 1H), 8.40 (s, 1H), 7.57 (dd, 1H), 7.51 (d, 1H), 7.50-7.42 (m, 2H), 6.98 (d, 1H), 3.61 (s, 2H), 3.32 (s, 2H), 3.11-3.01 (m, 2H), 2.94 (tt, 1H), 2.63-2.36 (m, 10H); ^{19}F NMR (376 MHz, d_6-dmso): δ -111.43 (dd, 1F); LCMS $(M+H)^+$: 496.3.

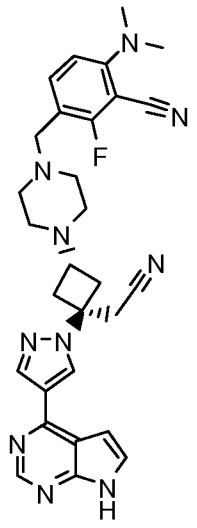
Example 2a. 3-[(4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)methyl]-6-(dimethylamino)-2-fluorobenzonitrile



To a solution of {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, from Example 1a, Step 9) and 6-(dimethylamino)-2-fluoro-3-

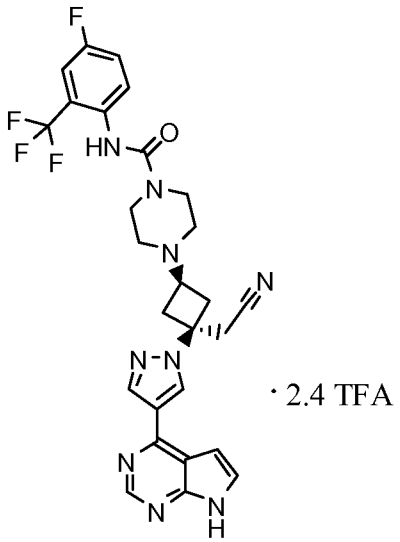
formylbenzonitrile (0.018 g, 0.091 mmol) in methylene chloride (1 mL) was added sodium triacetoxyborohydride (0.052 g, 0.24 mmol) and the reaction was stirred overnight. The reaction mixture was partitioned between 1N NaOH, brine and DCM. The layers were separated, and the aqueous layer was extracted with a further two portions of DCM. The combined organic extracts were dried over sodium sulfate, decanted and concentrated. The product was deprotected by stirring with 1:1 TFA:DCM for 2 hours. The solvent was then removed *in vacuo*, and the residue was stirred in a solution of methanol (1.5 mL) containing 0.3 mL ethylenediamine. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (0.015 g, 40%). ^1H NMR (400 MHz, $CDCl_3$): δ 9.50 (s, 1H), 8.81 (s, 1H), 8.34 (s, 1H), 8.28 (s, 1H), 7.36 (dd, 1H), 7.32 (t, 1H), 6.77 (dd, 1H), 6.57 (d, 1H), 3.50 (s, 2H), 3.12 (s, 2H). 3.08 (s, 6H), 2.87 (tt, 1H), 2.82-2.74 (m, 2H), 2.72-2.64 (m, 2H), 2.60-2.20 (br m, 8H); ^{19}F NMR (376 MHz, d_6-dmso): δ -112.00 (d, 1F); LCMS $(M+H)^+$: 539.3.

Example 2b. 3-[(4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)methyl]-6-(dimethylamino)-2-fluorobenzonitrile



The procedure as for Example 2a was followed, using {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, from Example 1b, Step 1) as starting material to afford product as the free base, in the same yield (0.015 g, 46%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.22 (s, 1H), 8.83 (s, 1H), 8.46 (s, 1H), 8.33 (s, 1H), 7.39 (dd, 1H), 7.35 (t, 1H), 6.79 (dd, 1H), 6.58 (d, 1H), 3.54 (s, 2H), 3.21 (s, 2H), 3.10 (s, 6H), 3.04-2.96 (m, 2H), 2.95-2.86 (m, 1H), 2.80-1.60 (br m, 10H); ^{19}F NMR (376 MHz, d_6-dmso): -112.08 (d, 1F); δ LCMS $(M+H)^+$: 539.0.

Example 3a. 4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[4-fluoro-2-(trifluoromethyl)phenyl]piperazine-1-carboxamide 2.4 x (trifluoroacetate) salt

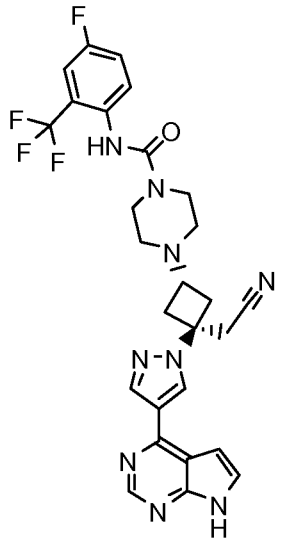


· 2.4 TFA

{cis-3-Piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.027 g, 0.055 mmol, prepared as in Example 1a, Step 9) was dissolved in tetrahydrofuran (2 mL) and triethylamine (23 μL, 0.16 mmol) followed by 4-fluoro-1-isocyanato-2-(trifluoromethyl)benzene (10 mg, 0.06 mmol, Aldrich) were added. The reaction was stirred for 1 hour. Solvent was removed *in vacuo*. The residue was stirred with TFA/DCM 1:1 for 1 hour, followed by evaporation and stirring with excess ethylenediamine in MeOH until the deprotection was complete. HPLC-MS (C18, eluting

with a gradient of H_2O/MeCN containing 0.1% TFA) was used to purify the product. The eluent containing the desired mass was frozen and lyophilized to afford product as the 2.4 x TFA salt (10 mg, 22%). ^{1}H NMR (300 MHz, d_6-dmso): δ 12.33 (br s, 1H), 8.86 (s, 1H), 8.76 (s, 1H), 8.62 (s, 1H), 8.49 (s, 1H), 7.69 (dd, 1H), 7.63 (dd, 1H), 7.55 (dd, 1H), 7.47 (dd, 1H), 7.11 (dd, 1H), 5.24-2.78 (m, 15H); ^{19}F NMR (282 MHz, d_6-dmso): δ -59.88 (s, 3F), -74.61 (s, 7.2F), -114.58 (dd, 1F); LCMS $(M+H)^+$: 568.3.

Example 3b. 4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[4-fluoro-2-(trifluoromethyl)phenyl]piperazine-1-carboxamide 2.3 x (trifluoroacetate) salt

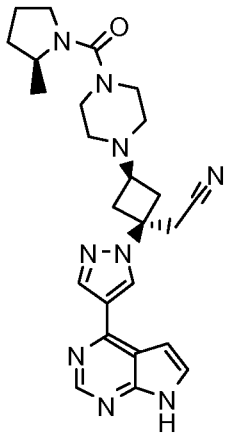


· 2.3 TFA

{trans-3-Piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.015 g, 0.030 mmol, prepared as in Example 1b, Step 1) was dissolved in tetrahydrofuran (1 mL) and triethylamine (13 μL, 0.091 mmol) followed by 4-fluoro-1-isocyanato-2-(trifluoromethyl)benzene (7 mg, 0.03 mmol, Aldrich) were added. The reaction was stirred for 1 hour. Solvent was removed *in vacuo*. The residue was stirred with 1:1 DCM;TFA for 1 hour, then with excess ethylenediamine in methanol HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.1% TFA) was used to purify the product. The eluent containing the desired mass was frozen and lyophilized to afford product as the 2.3 x trifluoroacetate salt (7 mg, 28%). ^{1}H NMR (300 MHz, d_6-dmso): δ

12.31 (br s, 1H), 8.97 (s, 1H), 8.75 (s, 1H), 8.60 (s, 1H), 8.51 (s, 1H), 7.68 (dd, 1H), 7.62 (dd, 1H), 7.58-7.50 (m, 1H), 7.45 (dd, 1H), 7.14 (dd, 1H), 5.57-2.73 (m, 15H); ^{19}F NMR (282 MHz, d_6-dmso): δ -59.91 (s, 3F), -74.58 (s, 6.9F), -114.62 (dd, 1F); LCMS $(M+H)^+$: 568.2.

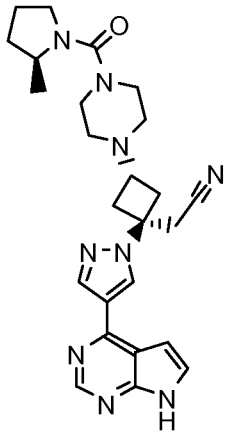
Example 4a. {cis-3-(4-{[(2S)-2-methylpyrrolidin-1-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



To a mixture of (2S)-2-methylpyrrolidine (0.0142 mL, 0.142 mmol) in methylene chloride (0.13 mL) and tetrahydrofuran (0.38 mL) was added triethylamine (0.099 mL, 0.710 mmol) followed by 1.89 M phosgene in toluene (0.113 mL, 0.213 mmol). The reaction mixture was stirred for 1 hour, followed by evaporation and hyvac to remove excess reagents. Triethylamine (0.040 mL, 0.28 mmol) was again added followed by acetonitrile (0.4 mL) and tetrahydrofuran (0.38 mL) . To this solution was added {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.035 g, 0.071 mmol, from Example 1a, Step 9) and the reaction was stirred overnight. The solvent was then removed *in vacuo*. The residue was stirred with 1:1 TFA:DCM for 2 hours, then evaporated and stirred with 0.2 mL ethylenediamine in methanol (1.5 mL) until the deprotection complete. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (0.007 g, 20%). ^{1}H NMR (300 MHz, d_6-dmso): δ 12.12 (br s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.39 (s, 1H), 7.60 (d, 1H),

7.06 (d, 1H), 3.89-3.78 (m, 1H), 3.47 (s, 2H), 3.36-2.99 (m, 6H), 2.92 (tt, 1H), 2.71-2.53 (m, 4H), 2.42-2.19 (m, 4H), 2.06-1.95 (m, 1H), 1.86-1.71 (m, 1H), 1.69-1.48 (m, 1H), 1.43-1.26 (m, 1H), 1.06 (d, 3H); LCMS $(M+H)^+$: 474.0.

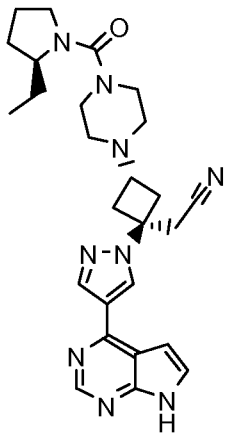
Example 4b. {trans-3-(4-{[(2S)-2-methylpyrrolidin-1-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



To a mixture of (2S)-2-methylpyrrolidine (0.0122 mL, 0.122 mmol) in methylene chloride (0.11 mL) and tetrahydrofuran (0.32 mL) was added triethylamine (0.0849 mL, 0.609 mmol) followed by 1.89 M phosgene in toluene (0.0966 mL, 0.183 mmol). The reaction mixture was stirred for 1 hour, followed by evaporation and hyvac to remove excess reagents. Triethylamine (0.0339 mL, 0.244 mmol) was again added followed by acetonitrile (0.3 mL) and tetrahydrofuran (0.32 mL) . To this solution was added {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, from Example 1b, Step 1) and the reaction was stirred overnight. The solvent was then removed *in vacuo*. The residue was stirred with 1:1 TFA:DCM for 2 hours, then evaporated and stirred with 0.2 mL ethylenediamine in methanol (1.5 mL) until the deprotection complete. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (0.007 g, 20%). ^1H NMR (300 MHz, d_6-dmso): δ 12.12 (br s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, 1H), 7.07 (d, 1H), 3.91-3.76 (m, 1H), 3.42 (s, 2H), 3.30-3.18 (m, 4H), 3.15-3.05 (m, 2H), 3.04-

2.94 (m, 2H), 2.78 (tt, 1H), 2.41-2.18 (m, 6H), 2.06-1.94 (m, 1H), 1.83-1.70 (m, 1H), 1.67-1.49 (m, 1H), 1.42-1.26 (m, 1H), 1.06 (d, 3H); LCMS $(M+H)^+$: 474.2.

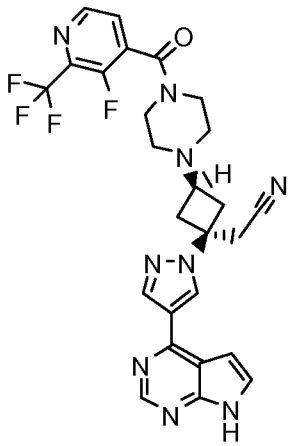
Example 5. {trans-3-(4-{[(2S)-2-ethylpyrrolidin-1-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



1.89 M Phosgene in toluene (0.0966 mL, 0.183 mmol) was added to a solution of triethylamine (0.0849 mL, 0.609 mmol) in methylene chloride (0.11 mL) and tetrahydrofuran (0.32 mL). A solution of (2S)-2-ethylpyrrolidine hydrochloride (0.0165 g, 0.122 mmol, prepared as described in Chemistry -- A European Journal, 12(28), 7398-7410; 2006 and WO2005/103020) in methylene chloride (0.7 mL) was added and the reaction mixture was stirred for 1 hour. {trans-3-Piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, prepared as in Example 1b, Step1) was added in a solution of acetonitrile (0.5 mL) . The reaction was stirred overnight. Solvent was removed *in vacuo*. The residue was stirred with 1:1 TFA:DCM for 2 hours, then evaporated and stirred with 0.2 mL ethylenediamine in methanol (1.5 mL) until deprotection was complete. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (0.01 g, 30%).

^{1}H NMR (300 MHz, d_6-dmso): δ 12.12 (br s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.41 (s, 1H), 7.60 (d, 1H), 7.07 (d, 1H), 3.86-3.75 (m, 1H), 3.42 (s, 2H), 3.32-3.18 (m, 4H), 3.15-2.94 (m, 4H), 2.78 (tt, 1H), 2.41-2.18 (m, 6H), 2.03-1.90 (m, 1H), 1.83-1.72 (m, 1H), 1.67-1.49 (m, 2H), 1.46-1.31 (m, 1H), 1.30-1.15 (m, 1H), 0.77 (t, 3H); LCMS $(M+H)^+$: 488.3.

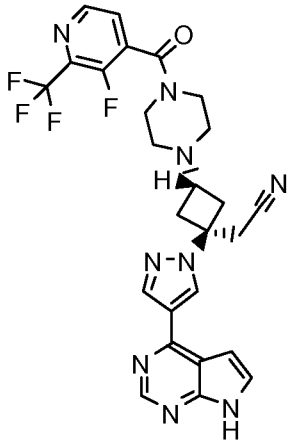
Example 6a. {cis-3-{4-[3-fluoro-2-(trifluoromethyl)isonicotinoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



To a mixture of 3-fluoro-2-(trifluoromethyl)isonicotinic acid (0.270 g, 1.29 mmol, Oakwood) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.636 g, 1.44 mmol, Advanced ChemTech) in N,N-dimethylformamide (5 mL) was added Triethylamine (0.417 mL, 2.99 mmol) and this was stirred for 10 minutes, followed by the addition of {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.590 g, 1.20 mmol, from Example 1a, Step 9) in a solution of N,N-dimethylformamide. The reaction was stirred overnight. Additional triethylamine (1.2 mL, 8 mmol), 3-fluoro-2-(trifluoromethyl)isonicotinic acid (0.270 g, 1.29 mmol) , and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.636 g, 1.44 mmol) were combined in N,N-dimethylformamide (5 mL, 60 mmol) on the side and the incomplete reaction mixture was added to it. After stirring for a few hours, the now complete reaction mixture was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The layers were separated, and the aqueous portion was extracted with ethyl acetate a total of three times. The combined organic extracts were dried over

sodium sulfate, decanted and concentrated. The crude product was deprotected by stirring with 1:1 TFA in DCM (40 mL) for 3 hours, then solvents were removed *in vacuo*. The deprotection was completed by stirring with excess ethylenediamine (2.4 mL total added in portions) in methanol (20 mL). The reaction mixture was partitioned between water and ethyl acetate. The aqueous portion was extracted three times. The combined extracts were washed with brine, dried over sodium sulfate, decanted and concentrated. Flash chromatography, eluting with a gradient from 0-10% MeOH in DCM was used to purify product. The product, as a glass, was reconstituted in MeCN/H_2O, frozen and lyophilized (260 mg, 39%). ^{1}H NMR (400 MHz, d_6-dmso): δ 12.13 (br s, 1H), 8.70 (s, 1H), 8.69-8.67 (m, 2H), 8.39 (s, 1H), 7.91 (t, 1H), 7.60 (dd, 1H), 7.06 (dd, 1H), 3.76-3.58 (m, 2H), 3.47 (s, 2H), 3.31-3.23 (m, 2H), 2.97 (tt, 1H), 2.70-2.55 (m, 4H), 2.47-2.20 (m, 4H); ^{19}F NMR (376 MHz, d_6-dmso): δ -64.52 (d, 3F), -129.01 (qd, 1F); LCMS $(M+H)^+$: 554.3.

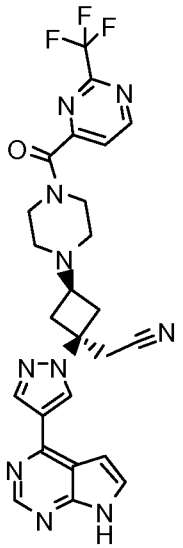
Example 6b. {trans-3-{4-[3-fluoro-2-(trifluoromethyl)isonicotinoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



A mixture of 3-fluoro-2-(trifluoromethyl)isonicotinic acid (0.331 g, 1.58 mmol, Oakwood), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.700 g, 1.58 mmol, Advanced ChemTech), and triethylamine (0.68 mL, 4.9 mmol) in N,N-dimethylformamide (6 mL) was prestirred for 10 minutes, followed by the addition of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.600 g, 1.22 mmol, from

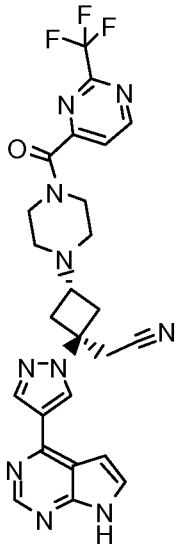
Example 1b, Step 1) in N,N-dimethylformamide (6 mL). The reaction was stirred overnight. The reaction mixture was partitioned between saturated sodium bicarbonate and ethyl acetate. The layers were separated and the aqueous portion was extracted with a further two portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate, decanted and concentrated. Flash chromatography, eluting with a gradient from 0-10% MeOH in DCM afforded SEM-protected intermediate. The product was deprotected by first stirring with trifluoroacetic Acid (5 mL) in methylene chloride (5 mL) for 4 hours, then evaporation, followed by stirring with ethylenediamine (1.63 mL, 24.4 mmol) in methanol (10 mL) until deprotection was complete. The reaction mixture was partitioned between water and ethyl acetate, and the aqueous portion extracted a total of three times with ethyl acetate. The combined organic extracts were dried over sodium sulfate, decanted and concentrated. Flash chromatography, eluting with a gradient from 0-10% MeOH/DCM was used to purify product. The product so obtained was re-purified by preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (0.2 g, 30%). ^{1}H NMR (300 MHz, CD_3OD): δ 8.70 (s, 1H), 8.66 (s, 1H), 8.61 (d, 1H), 8.39 (s, 1H), 7.75 (t, 1H), 7.51 (d, 1H), 6.98 (d, 1H), 3.90-3.81 (m, 2H), 3.43-3.37 (m, 2H), 3.34 (s, 2H), 3.13-3.02 (m, 2H), 2.96 (tt, 1H), 2.58-2.46 (m, 4H), 2.46-2.38 (m, 2H); ^{19}F NMR (282 MHz, CD_3OD): δ -67.40 (d, 3F), -129.37 (qd, 1F); LCMS $(M+H)^+$: 553.8.

Example 7a. [cis-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile



A solution of 2-(trifluoromethyl)pyrimidine-4-carboxylic acid (0.015 g, 0.076 mmol, prepared by hydrolysis of the methyl ester obtained from Apollo as described in WO2006/067445), N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.023 g, 0.061 mmol, Aldrich) and triethylamine (0.021 mL, 0.15 mmol) in tetrahydrofuran (0.5 mL) was prestirred, then to this was added {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.025 g, 0.051 mmol, from Example 1a, Step 9) in a solution of Tetrahydrofuran (1 mL). The reaction was stirred overnight, then was diluted with ethyl acetate, and saturated sodium bicarbonate and brine were added. The layers separated and the organic layer was washed with dilute HCl, dried over sodium sulfate, decanted and concentrated. The crude product was deprotected by stirring with 1:1 TFA:DCM for 2 hours, then solvents were evaporated and the deprotection was completed by stirring with excess ethylenediamine in methanol. The product was purified by preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (0.007 g, 20%). ^1H NMR (300 MHz, d_6-dmso): δ 12.12 (br s, 1H), 9.22 (d, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.39 (s, 1H), 8.00 (d, 1H), 7.60 (d, 1H), 7.06 (d, 1H), 3.72-3.63 (m, 2H), 3.47 (s, 2H), 3.39-3.32 (m, 2H), 2.97 (tt, 1H), 2.74-2.56 (m, 4H), 2.47-2.39 (m, 2H), 2.36-2.27 (m, 2H); ^{19}F NMR (282 MHz, d_6-dmso): δ -69.57 (s, 3F); LCMS $(M+H)^+$: 537.2.

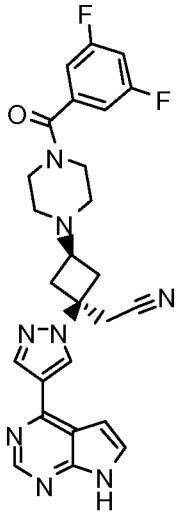
Example 7b. [trans-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile



A mixture of 2-(trifluoromethyl)pyrimidine-4-carboxylic acid (0.225 g, 1.17 mmol, prepared by hydrolysis of the methyl ester obtained from Apollo as described in WO2006/067445), N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.29 g, 0.76 mmol, Aldrich), and triethylamine (0.26 mL, 1.9 mmol) in tetrahydrofuran (6 mL) was prestirred for 15 minutes, followed by the addition of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.188 g, 0.380 mmol, prepared as in Example 1b, Step 1) in tetrahydrofuran (10 mL). The reaction was stirred overnight. THF was removed *in vacuo*. The residue was partitioned between saturated sodium bicarbonate and ethyl acetate. The aqueous portion was extracted a total of three times. The combined organic extracts were dried over sodium sulfate, decanted and concentrated. Flash chromatography, eluting with a gradient from 0-10% MeOH in DCM was used to purify the SEM-protected intermediate. Deprotection was effected by first stirring with trifluoroacetic acid (10 mL) in methylene chloride (10 mL) for 2 hours, followed by evaporation of solvent *in vacuo*, then stirring with methanol (6 mL, 200 mmol) containing ethylenediamine (0.5 mL, 7 mmol) overnight. The reaction mixture was partitioned between water and ethyl acetate, and the aqueous portion was extracted a

further two times with ethyl acetate. The combined extracts were dried over sodium sulfate, filtered and concentrated. Flash chromatography was used to purify product, eluting with a gradient from 0-10% MeOH in DCM. The product was repurified preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.1% TFA).Acetonitrile was removed from the eluent containing the desired mass via rotary evaporation, then the remaining aqueous solution was neutralized by the addition of sodium bicarbonate and extracted with ethyl acetate several times. The combined organic extracts were dried over sodium sulfate, filtered and concentrated. The product was re-purified by preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (99 mg, 48%). ^1H NMR (300 MHz, CD_3OD): δ 9.13 (d, 1H), 8.71 (s, 1H), 8.66 (s, 1H), 8.39 (s, 1H), 7.88 (d, 1H), 7.50 (d, 1H), 6.98 (d, 1H), 3.89-3.81 (m, 2H), 3.59-3.52 (m, 2H), 3.34 (s, 2H), 3.13-3.03 (m, 2H), 2.97 (tt, 1H), 2.59-2.42 (m, 6H); ^{19}F NMR (282 MHz, CD_3OD): δ -72.43 (s, 3F); LCMS $(M+H)^+$: 537.0.

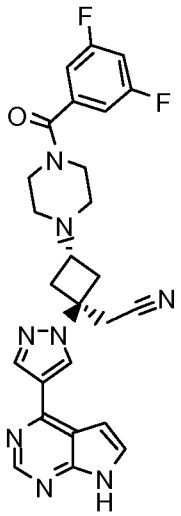
Example 8a. {cis-3-[4-(3,5-difluorobenzoyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



To a solution of 3,5-difluorobenzoyl chloride (54 mg, 0.30 mmol, Aldrich) and{cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-

d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.100 g, 0.203 mmol, from Example 1a, Step 9) in tetrahydrofuran (4 mL) was added triethylamine (0.085 mL, 0.61 mmol). The reaction was stirred overnight and solvent removed *in vacuo*. The product was then deprotected by stirring with 1:1 TFA:DCM for 2 hours, then evaporated and stirred with excess ethylenediamine in methanol until hydroxymethyl removal complete. The compound was then purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (16 mg, 16%). ^{1}H NMR (400 MHz, d_6-dmso): δ 8.70 (s, 1H), 8.68 (s, 1H), 8.39 (s, 1H), 7.60 (d, 1H), 7.36 (tt, 1H), 7.20-7.13 (m, 2H), 7.06 (d, 1H), 3.67-3.56 (br m, 2H), 3.47 (s, 2H), 3.32-3.23 (m, 2H), 2.95 (tt, 1H), 2.70-2.55 (m, 4H), 2.43-2.24 (m, 4H); ^{19}F NMR (376 MHz, d_6-dmso): δ -109.01 (dd, 2F); LCMS $(M+H)^+$: 503.2.

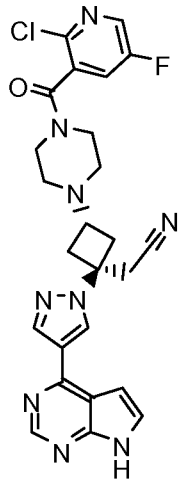
Example 8b. {trans-3-[4-(3,5-difluorobenzoyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



To a solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, from Example 1b, Step 1) in tetrahydrofuran (1 mL) was added triethylamine (0.025 mL, 0.18 mmol) followed by 3,5-difluorobenzoyl chloride (0.012 mL, 0.091 mmol, Aldrich). The reaction was stirred for a

few hours, then concentrated via rotary evaporation. The product was then deprotected by first stirring with 1:1 TFA:DCM for 1 hour, followed by evaporation and stirring with excess ethylenediamine in methanol until deprotection of SEM was complete. The compound was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (20 mg, 60%). ^{1}H NMR (300 MHz, d_6-dmso): δ 12.12 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (dd, 1H), 7.36 (tt, 1H), 7.21-7.12 (m, 2H), 7.07 (dd, 1H), 3.72-3.56 (m, 2H), 3.43 (s, 2H), 3.37-3.25 (m, 2H), 3.08-2.94 (m, 2H), 2.83 (tt, 1H), 2.46-2.24 (m, 6H); ^{19}F NMR (282 MHz, d_6-dmso): δ -109.00 (dd, 2F); LCMS $(M+H)^+$: 503.2.

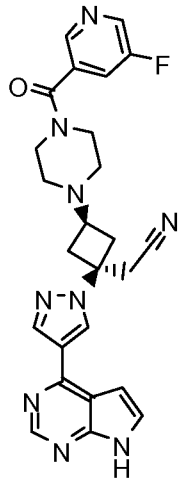
Example 9b. {trans-3-{4-[(2-chloro-5-fluoropyridin-3-yl)carbonyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



A mixture of 2-chloro-5-fluoronicotinic acid (0.027 g, 0.15 mmol, Matrix), triethylamine (0.041 g, 0.40 mmol) and N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.046 g, 0.12 mmol, Aldrich) in tetrahydrofuran (0.6 mL) was stirred for 10 minutes, followed by the addition of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.050 g, 0.10 mmol, from Example 1b, Step 1) in tetrahydrofuran (0.6 mL). The reaction was stirred for 3 hours, the solvent was evaporated, and the mixture was stirred with 1:1 TFA:DCM for 1 hour, followed by

evaporation and stirring with 0.2 mL ethylenediamine in methanol until deprotection complete. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (23 mg, 43%). ^1H NMR (300 MHz, d_6-dmso): δ 12.12 (br s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.55 (d, 1H), 8.41 (s, 1H), 8.04 (dd, 1H), 7.60 (d, 1H), 7.07 (d, 1H), 3.77-3.57 (m, 2H), 3.42 (s, 2H), 3.27-3.16 (m, 2H), 3.08-2.94 (m, 2H), 2.84 (tt, 1H), 2.45-2.23 (m, 6H); ^{19}F NMR (282 MHz, d_6-dmso): δ -128.62 (d, 1F); LCMS $(M+H)^+$: 520.1/522.1.

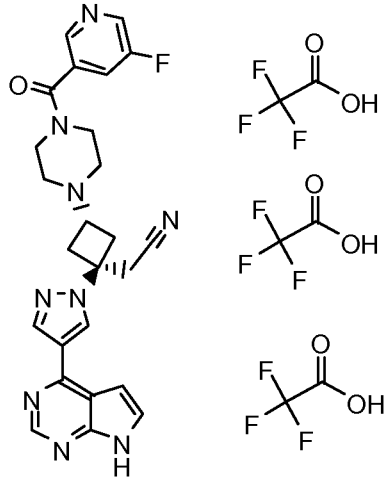
Example 10a. {cis-3-{4-[(5-fluoropyridin-3-yl)carbonyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



A mixture of 2-chloro-5-fluoronicotinic acid (0.027 g, 0.15 mmol, Matrix), triethylamine (0.041 g, 0.40 mmol) and N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.046 g, 0.12 mmol, Aldrich) in tetrahydrofuran (0.6 mL) was stirred for 10 minutes, followed by the addition of {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.050 g, 0.10 mmol, Example 1a, Step 9) in tetrahydrofuran (0.6 mL). The reaction was stirred for 3 hours, and was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was evaporated to afford the clean SEM-protected intermediate. This was hydrogenated under 55 psi of hydrogen overnight in a degassed

mixture of ethanol (5 mL) containing palladium on carbon (0.011 g, 0.010 mmol, 10%, wet Degussa type) and sodium bicarbonate (0.0259 g, 0.304 mmol). The reaction mixture was filtered, rinsed with ethanol and the solvent was removed *in vacuo*. The residue was then azeotroped once with toluene. The deprotection was effected by stirring with 1:1 TFA:DCM for 1 hour, evaporation, then stirring with 0.4 mL ethylenediamine in methanol until the deprotection was complete. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (0.01 g, 20%) ^{1}H NMR (400 MHz, d_6-dmso): δ 12.12 (br s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.67 (d, 1H), 8.49 (t, 1H), 8.39 (s, 1h), 7.85 (ddd, 1H), 7.60 (d, 1H), 7.06 (d, 1H), 3.64 (br, 2H), 3.47 (s, 2H), 3.37-3.28 (br, 2H), 2.96 (tt, 1H), 2.69-2.56 (m, 4H), 2.41 (br, 2H), 2.32 (br, 2H); ^{19}F NMR (376 MHz, d_6-dmso): δ -126.62 (dd, 1F); LCMS $(M+H)^+$: 486.4.

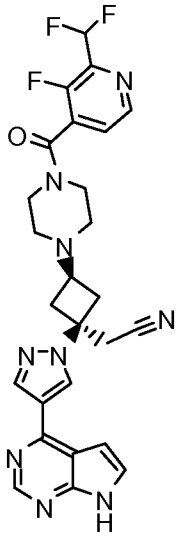
Example 10b. {trans-3-{4-[(5-fluoropyridin-3-yl)carbonyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile tris(trifluoroacetate) salt



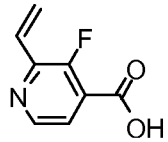
To a solution of {trans-3-{4-[(2-chloro-5-fluoropyridin-3-yl)carbonyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (18 mg, 0.035 mmol, from Example 9b) in ethanol (5 mL) was added sodium bicarbonate (0.0259 g, 0.304 mmol), and the mixture was degassed. Palladium on carbon (0.011 g,

0.010 mmol, 10% on carbon, wet, Degussa type) was added and the mixture stirred and shaken under 55 psi of hydrogen overnight. The reaction mixture was filtered, rinsed with methanol and evaporated, then purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.1% TFA). The eluent containing the desired mass was frozen and lyophilized to afford product as the 3 x TFA salt (5 mg, 10%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 8.85 (s, 1H), 8.48 (s, 1H), 8.37 (d, 1H), 8.36 (dd, 1H), 8.34 (s, 1H), 7.44 (ddd, 1H), 7.40 (d, 1H), 6.81 (dd, 1H), 3.56 (s, 2H), 3.22 (s, 2H), 3.05-2.96 (m, 2H), 2.92 (tt, 1H), 2.66-2.25 (m, 10H); ^{19}F NMR (282 MHz, d_6-dmso): δ -74.75 (s, 9F), -126.45 (d, 1F); LCMS $(M+H)^+$: 486.2.

Example 11a. {cis-3-{4-[2-(difluoromethyl)-3-fluoroisonicotinoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



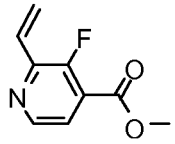
Step 1. 3-fluoro-2-vinylisonicotinic acid



A solution of 2-chloro-3-fluoroisonicotinic acid (1.50 g, 8.55 mmol, Matrix), dibutyl vinylboronate (2.82 mL, 12.8 mmol, Aldrich), and potassium carbonate (1.42 g, 10.25 mmol) in N,N-dimethylacetamide (9 mL) and water (3 mL) was degassed by

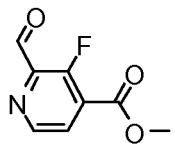
bubbling a stream of nitrogen through the solution for 20 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.59 g, 0.51 mmol) was added and the mixture was similarly degassed for a further 10 minutes. The reaction vessel was sealed and heated in the microwave for 25 minutes at 135 °C. The reaction mixture was filtered and purified using preparative HPLC (UV-detection) eluting with a gradient of H_2O/MeCN containing 0.1% TFA. This reaction was run again on the same scale and the product of both runs were pooled. Solvent was removed from the eluent containing desired product *in vacuo* (1.3 g, 46%). ^{1}H NMR (300 MHz, CD_3OD): δ 8.45 (d, 1H), 7.69 (dd, 1H), 7.07 (ddd, 1H), 6.44 (dd, 1H), 5.65 (dd, 1H); ^{19}F NMR (282 MHz, CD_3OD): δ -129.64 (d, 1F); LCMS $(M+H)^+$: 167.9.

Step 2. methyl 3-fluoro-2-vinylisonicotinate



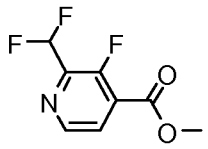
To a solution of 3-fluoro-2-vinylisonicotinic acid (1.3 g, 7.8 mmol, from Step 1) in methanol (20 mL) cooled to 0 °C, was added dropwise 2.0 M trimethylsilyldiazomethane in ether (21.6 mL, 44 mmol). When the reaction was complete, acetic acid was added dropwise to quench excess reagent and the volume of solvent was reduced *in vacuo*. The mixture was partitioned between saturated sodium bicarbonate solution and DCM. The aqueous portion was extracted with a total of three portions of DCM. The combined extracts were dried over sodium sulfate, decanted and concentrated and The product was used without further purification (1.4 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.47 (d, 1H), 7.62 (dd, 1H), 7.08 (ddd, 1H), 6.48 (dd, 1H), 5.65 (dd, 1H), 3.97 (s, 3H); LCMS $(M+H)^+$: 182.0.

Step 3. methyl 3-fluoro-2-formylisonicotinate



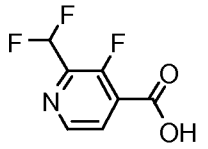
Ozone was bubbled through a solution of methyl 3-fluoro-2-vinylisonicotinate (1.4 g, 7.73 mmol, from Step 2) in methylene chloride (100 mL) at -78 °C until the blue color of excess ozone persisted. Nitrogen was bubbled through the solution for 1 minute to purge excess ozone and then triphenylphosphine (3.9 g, 15 mmol) was added and the solution was warmed to room temperature and stirred overnight. The compound was dry loaded onto silica gel. Flash chromatography eluting with 40% ethyl acetate in hexanes afforded product (0.8 g, 57%) as an off-white crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.27 (s, 1H), 8.73 (d, 1H), 8.01 (dd, 1H), 4.01 (s, 3H).

Step 4. methyl 2-(difluoromethyl)-3-fluoroisonicotinate



To a solution of methyl 3-fluoro-2-formylisonicotinate (0.80 g, 4.4 mmol, from Step 3) in methylene chloride (30 mL) and ethanol (0.06 mL) at 0 °C was added Deoxo-Fluor® (Aldrich (3 mL, 20 mmol). The reaction was continued at this temperature for 2 hours. Water was added into the cold reaction mixture. The product was extracted with three portions of DCM. The extracts were washed with water, dried over sodium sulfate, decanted and concentrated. The crude product was used without further purification (0.44 g, 49%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (d, 1H), 7.92 (dd, 1H), 6.85 (t, 1H), 4.00 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ -117.85 (dd, 2F), -125.97 (td, 1F).

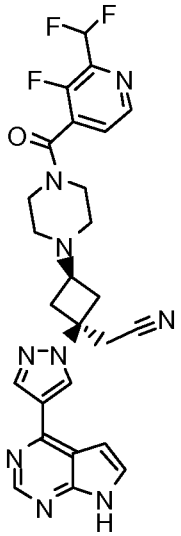
Step 5. 2-(difluoromethyl)-3-fluoroisonicotinic acid



To a solution of methyl 2-(difluoromethyl)-3-fluoroisonicotinate (0.44 g, 2.1 mmol, from Step 4) in tetrahydrofuran (10 mL) was added a solution of lithium hydroxide monohydrate (0.45 g, 11 mmol) in water (10 mL). The reaction was stirred for 2 hours. The reaction mixture was acidified by the addition of a solution of citric acid.

The product was extracted with three portions of DCM. The combined extracts were dried over sodium sulfate, decanted and concentrated to afford product, which was used without further purification in Step 6. ^{1}H NMR (300 MHz, CD_3OD): δ 8.57 (d, 1H), 7.99 (dd, 1H), 6.96 (t, 1H).

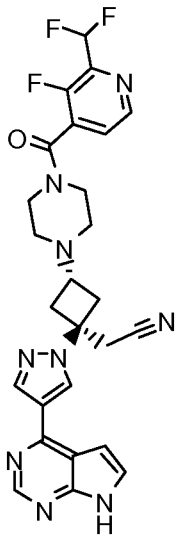
Step 6. {cis-3-{4-[2-(difluoromethyl)-3-fluoroisonicotinoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



To a prestirred combination of 2-(difluoromethyl)-3-fluoroisonicotinic acid (0.014 g, 0.076 mmol, from Step 5), N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.023 g, 0.061 mmol, Aldrich) and triethylamine (0.027 mL, 0.19 mmol) in tetrahydrofuran (1.5 mL) was added {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.025 g, 0.051 mmol, Example 1a, Step 9) as a solid. The reaction was stirred overnight. The mixture was diluted with ethyl acetate, and was washed with saturated sodium bicarbonate and brine, followed by dilute HCl. The organic portion was dried over sodium sulfate, decanted and concentrated. The crude product was deprotected by stirring with 1:1 TFA:DCM for 2 hours, then solvent was removed *in vacuo*, and the residue was stirred with excess ethylenediamine in methanol until the deprotection was complete. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent

containing the desired mass was frozen and lyophilized to afford product as the free base (0.007 g, 20%). ^{1}H NMR (300 MHz, d_6-dmso): δ 12.08 (br s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.61 (d, 1H), 8.39 (s, 1H), 7.74 (dd, 1H), 7.60 (d, 1H), 7.19 (t, 1H), 7.05 (d, 1H), 3.67 (br, 2H), 3.47 (s, 2H), 3.28-3.20 (m, 2H), 2.97 (tt, 1H), 2.70-2.54 (m, 4H), 2.41 (br, 2H), 2.30 (br, 2H); ^{19}F NMR (282 MHz, d_6-dmso): δ -117.95 (dd, 2F), -131.83 - -131.97 (m, 1F); LCMS $(M+H)^+$: 536.3.

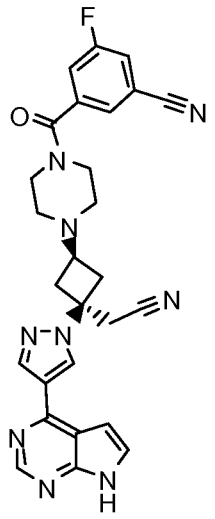
Example 11b. {trans-3-{4-[2-(difluoromethyl)-3-fluoroisonicotinoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



A mixture of 2-(difluoromethyl)-3-fluoroisonicotinic acid (0.34 g, 1.8 mmol, from Example 11a, Step 5), N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.72 g, 1.9 mmol, Aldrich) and triethylamine (0.81 mL, 5.8 mmol) in tetrahydrofuran (20 mL) was prestirred for 15 min, then to this was added {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.581 g, 1.18 mmol, prepared as in Example 1b, Step 1) in a solution of tetrahydrofuran (30 mL). The reaction was stirred overnight, and then THF was removed *in vacuo*. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The layers were separated and the aqueous was extracted with two further portions of ethyl acetate. The combined organic extracts were washed with brine, then dried over sodium sulfate, decanted and concentrated. Flash

chromatography, eluting with a gradient from 0-10% MeOH in DCM afforded the SEM-protected intermediate. Deprotection was effected by stirring with 1:1 TFA:DCM for 2hours, then removal of solvent *in vacuo* followed by stirring with excess ethylenediamine in methanol until deprotection complete. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (0.137 g, 22%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.70 (s, 1H), 8.66 (s, 1H), 8.56 (d, 1H), 8.39 (d, 1H), 7.63 (dd, 1H), 7.50 (d, 1H), 6.97 (d, 1H), 6.94 (t, 1H), 3.85 (dd, 2H), 3.38 (dd, 2H), 3.34 (s, 2H), 3.10-3.02 (m, 2H), 2.95 (tt, 1H), 2.55-2.46 (m, 4H), 2.41 (dd, 2H); ^{19} F NMR (376 MHz, CD_3OD): δ -119.68 (ddd, 2F), -132.42 (td, 1F); LCMS $(M+H)^+$: 536.0.

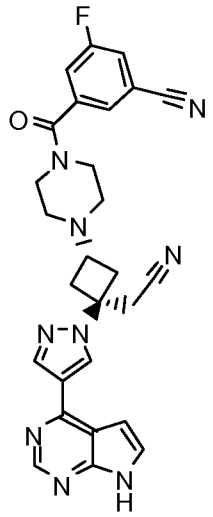
Example 12a. 3-[(4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)carbonyl]-5-fluorobenzonitrile



3-Cyano-5-fluorobenzoic acid (12 mg, 0.076 mmol, Oakwood) was coupled with {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.025 g, 0.051 mmol, prepared as in Example 1a, Step 9) by the procedure outlined in Step 6 of Example 11a, to afford 3-[(4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)carbonyl]-5-fluorobenzonitrile as the free base (11 mg,

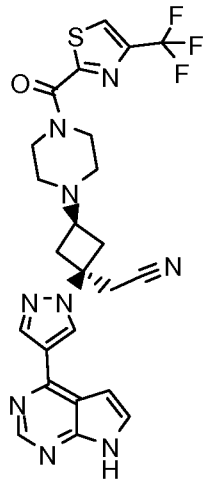
41%). ^{1}H NMR (400 MHz, d_6-dmso): δ 12.08 (br s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.40 (s, 1H), 7.97 (ddd, 1H), 7.78 (t, 1H), 7.69 (ddd, 1H), 7.60 (d, 1H), 7.06 (d, 1H), 3.69-3.56 (m, 2H), 3.50-3.22 (br m, 4H), 2.96 (tt, 1H), 2.69-2.56 (m, 4H), 2.44-2.24 (br m, 4H); ^{19}F NMR (376 MHz, d_6-dmso): δ -109.87 (t, 1F); LCMS $(M+H)^+$: 509.9.

Example 12b. 3-[(4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)carbonyl]-5-fluorobenzonitrile



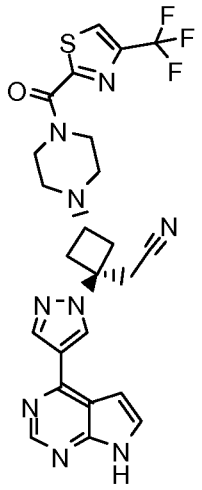
The procedure of Example 11a, Step 6 was followed, using {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, prepared as in Example 1b, Step 1) and 3-cyano-5-fluorobenzoic acid (0.015 g, 0.091 mmol, Oakwood) to afford product (0.01 g, 30%). ^{1}H NMR (300 MHz, d_6-dmso): δ 12.12 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.97 (ddd, 1H), 7.78 (s, 1H), 7.69 (ddd, 1H), 7.60 (d, 1H), 7.07 (d, 1H), 3.71-3.57 (m, 2H), 3.42 (s, 2H), 3.35-3.25 (m, 2H), 3.07-2.94 (m, 2H), 2.84 (tt, 1H), 2.46-2.24 (m, 6H); ^{19}F NMR (282 MHz, d_6-dmso): δ -109.86 (t, 1F); LCMS $(M+H)^+$: 510.2.

Example 13a. [cis-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile



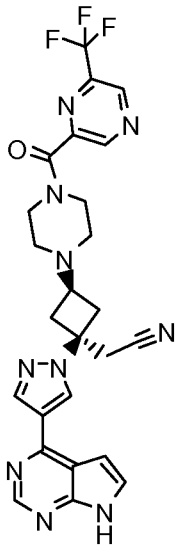
Using 4-(trifluoromethyl)-1,3-thiazole-2-carboxylic acid (15 mg, 0.076 mmol, SynQuest), and {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.025 g, 0.051 mmol, prepared as in Example 1a, Step 9) by the procedure analogous to Example 11a, Step 6, afforded [cis-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile (10 mg, 38%). ^{1}H NMR (400 MHz, d_6-dmso): δ 12.11 (br s, 1H), 8.79 (d, 1H), 8.71 (s, 1H), 8.69 (s, 1H), 8.40 (s, 1H), 7.60 (d, 1H), 7.06 (d, 1H), 4.24-4.13 (m, 2H), 3.72-3.63 (m, 2H), 3.48 (s, 2H), 2.96 (tt, 1H), 2.71-2.56 (m, 4H), 2.48-2.39 (m, 4H); ^{19}F NMR (376 MHz, d_6-dmso): δ -62.71 (s, 3F); LCMS $(M+H)^+$: 541.8.

Example 13b. [trans-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile



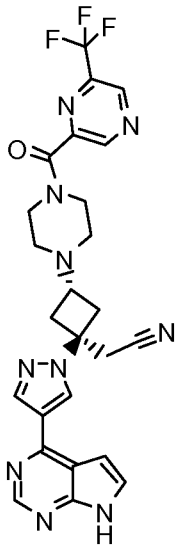
To a solution of 4-(trifluoromethyl)-1,3-thiazole-2-carboxylic acid (0.021 g, 0.11 mmol, SynQuest), Triethylamine (0.038 mL, 0.27 mmol) and N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.032 g, 0.085 mmol) in tetrahydrofuran (0.5 mL) was added {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.035 g, 0.071 mmol, prepared as in Example 1b, Step 1) as a solution in an aliquot of tetrahydrofuran (0.5 mL). The reaction was worked up by a partition between 1N NaOH and ethyl acetate. The aqueous portion was extracted with ethyl acetate three times. The combined organic extracts were dried over sodium sulfate, decanted and concentrated. The product was deprotected by stirring with 1:1 TFA:DCM for 2 hours, followed by removal of solvent *in vacuo*, then stirred with ethylenediamine 0.2 mL in methanol until deprotection was complete. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (0.007 g, 20%). ^{1}H NMR (300 MHz, d_6-dmso): δ 8.82 (s, 1H), 8.77 (d, 1H), 8.68 (s, 1H), 8.42 (s, 1H), 7.59 (d, 1H), 7.07 (d, 1H), 4.27-4.16 (m, 2H), 3.75-3.66 (m, 2H), 3.43 (s, 2H), 3.07-2.97 (m, 2H), 2.85 (tt, 1H), 2.48-2.34 (m, 6H); ^{19}F NMR (282 MHz, d_6-dmso): δ -62.73 (s, 3F); LCMS $(M+H)^+$: 542.2.

Example 14a. [cis-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[6-(trifluoromethyl)pyrazin-2-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile



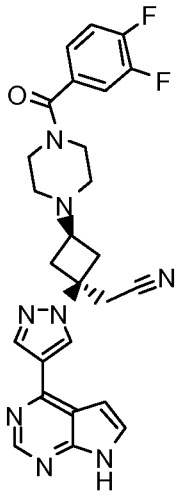
A solution of 6-(trifluoromethyl)pyrazine-2-carboxylic acid (15 mg, 0.076 mmol, Anichem), and {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.025 g, 0.051 mmol, prepared as in Example 1a, Step 9) were coupled and purified according to the procedure described for Example 11a, Step 6, to afford the product as the free base (7 mg, 20%). ^{1}H NMR (300 MHz, d_6-dmso): δ 12.12 (br s, 1H), 9.30 (s, 1H), 9.20 (s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.40 (s, 1H), 7.60 (d, 1H), 7.06 (d, 1H), 3.75-3.65 (m, 2H), 3.48 (s, 2H), 3.46-3.40 (m, 2H), 2.97 (tt, 1H), 2.72-2.55 (m, 4H), 2.48-2.39 (m, 2H), 2.37-2.29 (m, 2H); ^{19}F NMR (282 MHz, d_6-dmso): δ -66.71 (s, 3F); LCMS $(M+H)^+$: 537.2.

Example 14b. [trans-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[6-(trifluoromethyl)pyrazin-2-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile



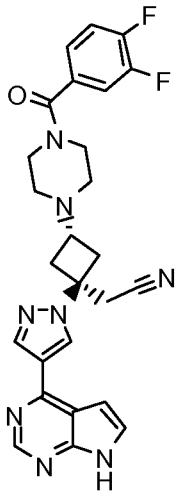
A solution of 6-(trifluoromethyl)pyrazine-2-carboxylic acid (12 mg, 0.061 mmol, Anichem), and {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.025 g, 0.051 mmol, prepared as in Example 1b, Step 1) were coupled and purified according to the procedure described for Example 11a, Step 6, to afford the product as the free base (6 mg, 30%). ^{1}H NMR (300 MHz, d_6-dmso): δ 12.12 (br s, 1H), 9.30 (s, 1H), 9.20 (s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, 1H), 7.07 (d, 1H), 3.77-3.68 (m, 2H), 3.50-3.44 (m, 2H), 3.43 (s, 2H), 3.08-2.95 (m, 2H), 2.85 (tt, 1H), 2.48-2.29 (m, 6H); ^{19}F NMR (282 MHz, d_6-dmso): δ -66.71 (s, 3F); LCMS $(M+H)^+$: 536.8.

Example 15a. {cis-3-[4-(3,4-difluorobenzoyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



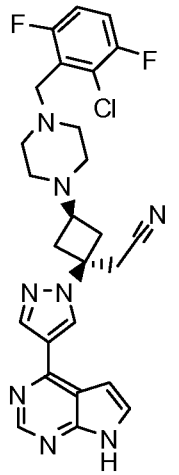
To a solution of {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, prepared as in Example 1a, Step 9) in tetrahydrofuran (1 mL) was added triethylamine (0.025 mL, 0.18 mmol) followed by 3,4-difluorobenzoyl chloride (0.011 mL, 0.091 mmol, Aldrich) . The reaction was stirred overnight, and then solvent was removed *in vacuo*. The crude product was deprotected by stirring with 1:1 TFA:DCM for 2 hours, then removal of solvent *in vacuo*, followed by stirring with excess ethylenediamine (0.2 mL) in methanol for 2 hours. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (0.01 g, 30%). ^{1}H NMR (400 MHz, d_6-dmso): δ 12.11 (br s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.39 (s, 1H), 7.60 (d, 1H), 7.56-7.47 (m, 2H), 7.29-7.24 (m, 1H), 7.06 (d, 1H), 3.61 (br, 2H), 3.47 (s, 2H), 3.40-3.26 (br, 2H), 2.95 (tt, 1H), 2.69-2.55 (m, 4H), 2.44-2.21 (br m, 4H); ^{19}F NMR (376 MHz, d_6-dmso): δ -137.34 (dddd, 1F), -138.23 (ddd, 1F); LCMS $(M+H)^+$: 503.1.

Example 15b. {trans-3-[4-(3,4-difluorobenzoyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



The procedure of Example 15a was followed, on the same scale, using {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (prepared as in Example 1b, Step 1) to afford product as the free base (0.01 g, 30%). ^{1}H NMR (400 MHz, d_6-dmso): δ 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, 1H), 7.56-7.46 (m, 2H), 7.29-7.24 (m, 1H), 7.07 (d, 1H), 3.63 (br, 2H), 3.42 (s, 2H), 3.40-3.27 (br, 2H), 3.05-2.97 (m, 2H), 2.83 (tt, 1H), 2.43-2.22 (m, 6H); ^{19}F NMR (376 MHz, d_6-dmso): δ -137.32 (dddd, 1F), -138.22 (ddd, 1F); LCMS $(M+H)^+$: 503.1.

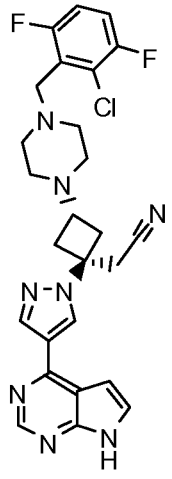
Example 16a. {cis-3-[4-(2-chloro-3,6-difluorobenzyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



To a solution of {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-

7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, prepared as in Example 1a, Step 9) and 2-chloro-3,6-difluorobenzaldehyde (0.016 g, 0.091 mmol) in methylene chloride (1 mL) was added sodium triacetoxyborohydride (0.052 g, 0.24 mmol) and the reaction was stirred overnight. The reaction mixture was partitioned between 1N NaOH, brine and DCM. The aqueous portion was extracted with three portions of DCM. The combined extracts were dried over sodium sulfate, decanted and concentrated. The crude product was deprotected by stirring with 1:1 TFA:DCM for 2 hours. Solvent was then removed *in vacuo*, and the residue was stirred with 0.3 mL ethylenediamine in methanol until the deprotection was complete. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (0.015 g, 47%). ^1H NMR (400 MHz, d_6-dmso): δ 12.11 (br s, 1H), 8.68 (s, 2H), 8.38 (s, 1H), 7.60 (d, 1H), 7.44 (ddd, 1H), 7.30 (ddd, 1H), 7.05 (d, 1H), 3.61 (s, 2H), 3.45 (s, 2H), 2.87 (tt, 1H), 2.61-2.13 (m, 12H); ^{19}F NMR (376 MHz, d_6-dmso): δ -117.52 - -117.64 (m, 1F), -118.99 (ddd, 1F); LCMS $(M+H)^+$: 523.2/525.2.

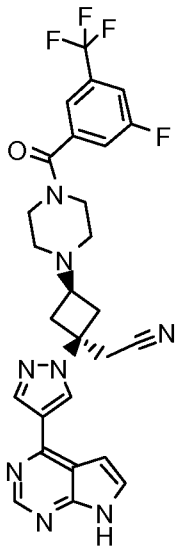
Example 16b. {trans-3-[4-(2-chloro-3,6-difluorobenzyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



The procedure of Example 16a was followed, on the same scale, using {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-

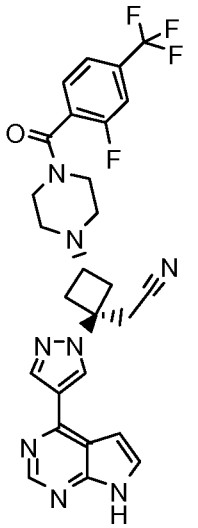
yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, prepared as in Example 1b, Step 1) to afford product as the free base (0.015 g, 47%). ^{1}H NMR (400 MHz, d_6-dmso): δ12.11 (br s, 1H), 8.80 (s, 1H), 8.68 (s, 1H), 8.40 (s, 1H), 7.59 (d, 1H), 7.45 (td, 1H), 7.30 (td, 1H), 7.06 (d, 1H), 3.62 (s, 2H), 3.40 (s, 2H), 3.50-2.92 (m, 2H), 2.74 (tt, 1H), 2.58-2.18 (m, 10H) ; ^{19}F NMR (376 MHz, d_6-dmso): δ -117.46 - -117.65 (m, 1F), -118.89 - -119.07 (m, 1F); LCMS $(M+H)^+$: 522.9.

Example 17. {cis-3-{4-[3-fluoro-5-(trifluoromethyl)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



The procedure of Example 15a was followed, using 3-fluoro-5-(trifluoromethyl)benzoyl chloride (17 mg, 0.076 mmol, Aldrich) and {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.025 g, 0.051 mmol, prepared as in Example 1a, Step 9) to afford product as the free base (11 mg, 40%). ^{1}H NMR (400 MHz, d_6-dmso): δ 12.12 (br s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.39 (s, 1H), 7.83-7.79 (m, 1H), 7.68-7.64 (m, 1H), 7.63 (br s, 1H), 7.60 (d, 1H), 7.06 (d, 1H), 3.64 (br, 2H), 3.47 (s, 2H), 3.29 (br, 2H), 2.96 (tt, 1H), 2.68-2.56 (m, 4H), 2.41 (br, 2H), 2.30 (br, 2H); ^{19}F NMR (376 MHz, d_6-dmso): δ -61.61 (s, 3F), -109.91 (dd, 1F); LCMS $(M+H)^+$: 553.0.

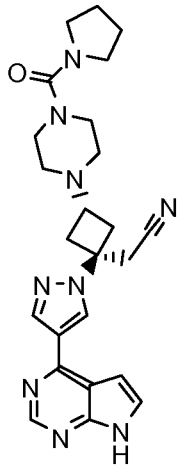
Example 18. {trans-3-{4-[2-fluoro-4-(trifluoromethyl)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile 2.3 x (trifluoroacetate) salt



· 2.3 TFA

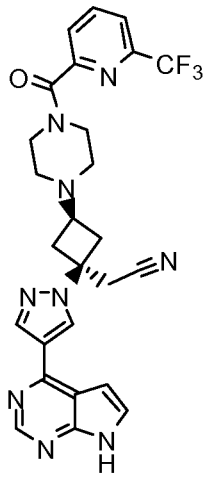
To a solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.033 g, 0.067 mmol, prepared as in Example 1b, Step 1) and triethylamine (0.0373 mL, 0.268 mmol) in acetonitrile (0.5 mL) was added 2-fluoro-4-(trifluoromethyl)benzoyl chloride (0.018 g, 0.080 mmol, Aldrich). The reaction was stirred for 2 hours, then was worked up by partition between 1 N NaOH and ethyl acetate. The organic layer was dried over sodium sulfate, decanted and concentrated. The crude product was deprotected by stirring with 1:1 DCM: TFA for 1 hour, followed by removal of solvents *in vacuo*, and stirring with excess ethylenediamine in methanol. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.1% TFA). The eluent containing the desired mass was frozen and lyophilized to afford product as the 2.3 x TFA salt (0.01 g, 20%). ^{1}H NMR (400 MHz, d_6-dmso): δ 12.41 (s, 1H), 8.98 (s, 1H), 8.77 (s, 1H), 8.51 (s, 1H), 7.87 (d, 1H), 7.74-7.72 (m, 2H), 7.71 (dd, 1H), 7.16 (dd, 1H), 3.96-2.73 (m, 15H); ^{19}F NMR (376 MHz, d_6-dmso): δ -61.78 (s, 3F), -74.59 (s, 6.9 F), -113.97 (br s, 1F); LCMS $(M+H)^+$: 553.3.

Example 19. {trans-3-[4-(pyrrolidin-1-ylcarbonyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



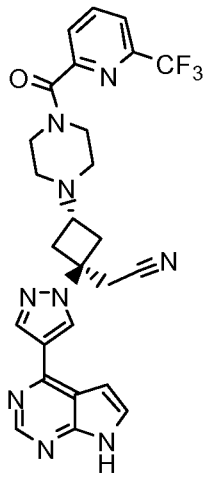
To a solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.035 g, 0.071 mmol, prepared as in Example 1b, Step 1) and Triethylamine (0.030 mL, 0.21 mmol) in Methylene chloride (1 mL) was added 1-pyrrolidinecarbonyl chloride (0.010 mL, 0.092 mmol, Aldrich). After stirring overnight, solvent was removed *in vacuo*. The residue was stirred with 1:1 TFA:DCM for 2 hours, then solvents were again evaporated and the residue stirred with 0.2 mL ethylenediamine in methanol until the deprotection was complete. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (0.007 g, 20%). ^{1}H NMR (300 MHz, d_6-dmso): δ 12.11 (br s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.41 (s, 1H), 7.60 (d, 1H), 7.07 (d, 1H), 3.42 (s, 2H), 3.38-3.10 (m, 8H), 3.06-2.93 (m, 2H), 2.78 (tt, 1H), 2.44-2.23 (m, 6H), 1.79-1.67 (m, 4H); LCMS $(M+H)^+$: 460.0.

Example 20a. {cis-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)cyclobutyl}acetonitrile



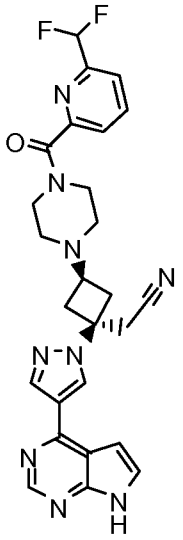
The method of Example 11a, Step 6 was followed, using 6-(trifluoromethyl)pyridine-2-carboxylic acid (0.014 g, 0.076 mmol, Matrix) and {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.025 g, 0.051 mmol, prepared as in Example 1a, Step 9) to afford product as the free base (0.007 g, 20%). ^{1}H NMR (300 MHz, d_6-dmso): δ 12.11 (br s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.39 (s, 1H), 8.24 (t, 1H), 8.01 (dd, 1H), 7.90 (d, 1H), 7.60 (d, 1H), 7.06 (d, 1H), 3.72-3.62 (m, 2H), 3.48 (s, 2H), 3.40-3.28 (m, 2H), 2.96 (tt, 1H), 2.70-2.55 (m, 4H), 2.47-2.39 (m, 2H), 2.36-2.25 (m, 2H); ^{19}F NMR (282 MHz, d_6-dmso): δ -66.96 (s, 3F); LCMS $(M+H)^+$: 536.2.

Example 20b. {trans-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)cyclobutyl}acetonitrile

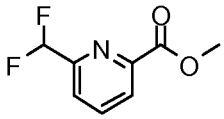


The method of Example 11a was followed, using 6-(trifluoromethyl)pyridine-2-carboxylic acid (0.012 g, 0.061 mmol, Matrix) and {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.020 g, 0.040 mmol, prepared as in Example 1b, Step 1) to afford product as the free base (0.006 g, 30%). ^{1}H NMR (300 MHz, d_6-dmso): δ 12.13 (br s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 8.24 (t, 1H), 8.01 (d, 1H), 7.90 (d, 1H), 7.60 (d, 1H), 7.07 (d, 1H), 3.76-3.65 (m, 2H), 3.43 (s, 2H), 3.42-3.36 (m, 2H), 3.07-2.94 (m, 2H), 2.84 (tt, 1H), 2.47-2.24 (m, 6H); ^{19}F NMR (282 MHz, d_6-dmso): δ -66.95 (s, 3F); LCMS $(M+H)^+$: 535.9.

Example 21a. {cis-3-(4-{[6-(difluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



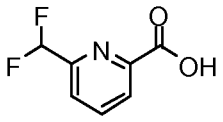
Step 1. methyl 6-(difluoromethyl)pyridine-2-carboxylate



To a solution of methyl 6-formylpyridine-2-carboxylate (1.00 g, 6.06 mmol) (ChemBridge Building Blocks) in methylene chloride (35 mL) containing a small amount of ethanol (0.1 mL) at 0 °C was added Deoxo-Fluor® (4.46 mL, 24.2 mmol, Aldrich). After 3 hours, the reaction was cooled in an ice bath and quenched by the addition of

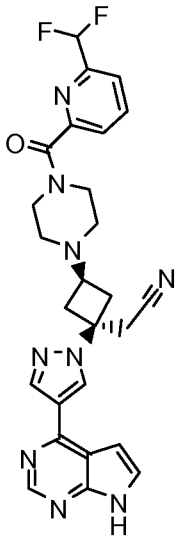
water. The product was extracted with three portions of DCM. The combined extracts were washed with water, dried over sodium sulfate, decanted and concentrated, to afford product which was used without further purification (1.1 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27-8.22 (m, 1H), 8.02 (t, 1H), 7.85 (dd, 1H), 6.75 (t, 1H), 4.03 (s, 3H); LCMS $(M+H)^+$: 187.9.

Step 2. 6-(difluoromethyl)pyridine-2-carboxylic acid



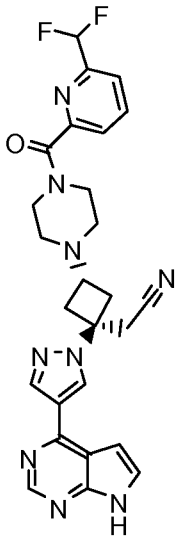
To a solution of methyl 6-(difluoromethyl)pyridine-2-carboxylate (0.58 g, 3.1 mmol, from Step 1) in Water (22 mL) and Tetrahydrofuran (20 mL, 250 mmol) was added Lithium hydroxide, monohydrate (0.65 g, 15 mmol). The reaction was stirred for 2 hours. The basic mixture was extracted with ether, which was discarded. The mixture was then acidified by the addition of 1 N HCl and the volume of solvent reduced *in vacuo*. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.1% TFA). The eluent containing the desired mass was evaporated by rotary evaporation to afford a solid product (0.35 g, 65%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.27 (ddd, 1H), 8.17 (dd, 1H), 7.92 (dd, 1H), 6.78 (t, 1H); ^{1}H NMR (400 MHz, CD_3OD): δ -117.52 (d, 2F); LCMS $(M+H)^+$: 173.9.

Step 3. {cis-3-(4-{[6-(difluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



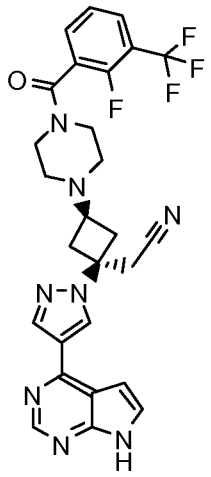
The procedure of Example 11a (Step 6) was followed, using 6-(difluoromethyl)pyridine-2-carboxylic acid (0.016 g, 0.091 mmol, from Step 2) and {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, prepared as in Example 1a, Step 9), except that in the work up after coupling, dilute HCl wash was omitted. The purification afforded product as the free base (0.01 g, 30%). ^{1}H NMR (300 MHz, CD_3OD): δ 8.66 (s, 1H), 8.64 (s, 1H), 8.37 (s, 1H), 8.11 (dd, 1H), 7.76 (dd, 1H), 7.51 (d, 1H), 6.98 (d, 1H), 6.73 (t, 1H), 3.86-3.77 (m, 2H), 3.60-3.49 (m, 2H), 3.34 (s, 2H), 3.01 (tt, 1H), 2.89-2.76 (m, 2H), 2.76-2.65 (m, 2H), 2.61-2.52 (m, 2H), 2.51-2.42 (m, 2H); ^{19}F NMR (282 MHz, CD_3OD): δ -118.19 (d, 2F); LCMS $(M+H)^+$: 517.9.

Example 21b. {trans-3-(4-{[6-(difluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



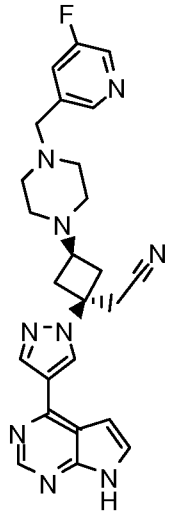
The procedure of Example 11a (Step 6) was followed, using 6-(difluoromethyl)pyridine-2-carboxylic acid (0.016 g, 0.091 mmol, Example 21a, Step 2) and{trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, prepared as in Example 1b, Step 1) except that in the workup after coupling, the dilute HCl wash was omitted. The purification afforded product as the free base (0.01 g, 30%). ^{1}H NMR (400 MHz, d_6-dmso): δ 12.11 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 8.13 (dd, 1H), 7.79 (d, 1H), 7.75 (d, 1H), 7.60 (d, 1H), 7.07 (d, 1H), 6.98 (t, 1H), 3.73-3.66 (m, 2H), 3.43 (s, 2H), 3.41-3.37 (m, 2H), 3.05-2.96 (m, 2H), 2.84 (tt, 1H), 2.46-2.27 (m, 6H); ^{19}F NMR (376 MHz, d_6-dmso): δ -116.20 (d, 2F); LCMS $(M+H)^+$: 517.8.

Example 22. {cis-3-{4-[2-fluoro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



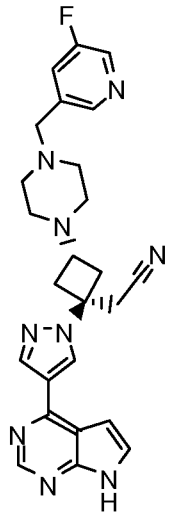
The procedure of Example 8b was followed, using {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (25 mg, 0.051 mmol, from Example 1a, Step 9) and 2-fluoro-3-(trifluoromethyl)benzoyl chloride (23 mg, 0.101 mmol). Purification afforded product as the free base (15 mg, 54%). ^{1}H NMR (300 MHz, d_6-dmso): δ 12.10 (br s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.39 (s, 1H), 7.88 (ddd, 1H), 7.77 (ddd, 1H), 7.60 (d, 1H), 7.50 (dd, 1H), 7.06 (d, 1H), 3.67 (br, 2H), 3.47 (s, 2H), 3.26-3.19 (m, 2H), 2.96 (tt, 1H), 2.69-2.54 (m, 4H), 2.40 (br s, 2H), 2.29 (br s, 2H); LCMS $(M+H)^+$: 553.3.

Example 23a. {cis-3-{4-[(5-fluoropyridin-3-yl)methyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



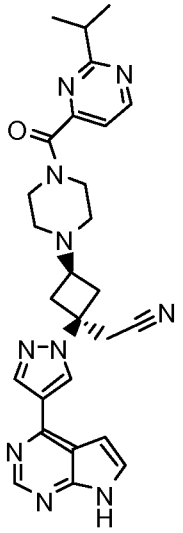
{cis-3-Piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, prepared as in Example 1a, Step 9) and 5-fluoronicotinaldehyde (0.011 g, 0.085 mmol) were combined in methylene chloride (1 mL) and after 10 minutes, sodium triacetoxyborohydride (0.0516 g, 0.244 mmol) was added. The reaction was continued overnight. The reaction mixture was partitioned between water and ethyl acetate. The aqueous portion was extracted a further two times with ethyl acetate. The combined extracts were washed with water, then brine, dried over sodium sulfate, decanted and concentrated. The crude product was deprotected by first stirring the residue in a 1:1 mix of TFA:DCM (4 mL) for 2 hours, followed by removal of the solvents *in vacuo* and then stirring with 0.2 mL ethylenediamine in 2 mL methanol overnight. The solution was filtered and the product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (0.01 g, 30%). ^1H NMR (400 MHz, $CDCl_3$): δ 10.13 (br s, 1H), 8.82 (s, 1H), 8.37 (d, 1H), 8.35 (dd, 1H), 8.33 (s, 1H), 8.27 (s, 1H), 7.43 (ddd, 1H), 7.37 (dd, 1H), 6.76 (dd, 1H), 3.54 (s, 2H), 3.13 (s, 2H), 2.89 (tt, 1H), 2.84-2.76 (m, 2H), 2.75-2.67 (m, 2H), 2.64-2.27 (br, 8H); ^{19}F NMR (376 MHz, d_6-dmso): δ -128.43 (dd, 1F); LCMS $(M+H)^+$: 472.5.

Example 23b. {trans-3-{4-[(5-fluoropyridin-3-yl)methyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



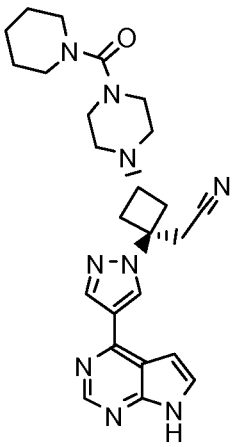
The procedure of Example 23a was followed, using {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, prepared as in Example 1b, Step 1) and 5-fluoronicotinaldehyde (0.011 g, 0.085 mmol). Purification by the same method afforded product as the free base (0.01 g, 30%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (br s, 1H), 8.85 (s, 1H), 8.48 (s, 1H), 8.37 (d,1H), 8.36 (dd, 1H), 8.34 (s, 1H), 7.44 (ddd, 1H), 7.40 (dd, 1H), 6.81 (dd, 1H), 3.56 (s, 2H), 3.22 (s, 2H), 3.05-2.96 (m, 2H), 2.92 (tt, 1H), 2.68-2.22 (m, 10H); ^{19}F NMR (376 MHz, d_6-dmso): δ -128.41 (dd, 1F); LCMS $(M+H)^+$: 472.5.

Example 24a. {cis-3-{4-[(2-isopropylpyrimidin-4-yl)carbonyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



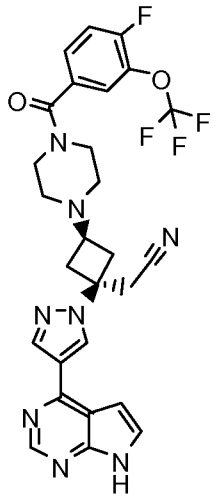
Step 3 of Example 21a was followed, using 2-isopropylpyrimidine-4-carboxylic acid (0.013 g, 0.076 mmol, ChemBridge), and {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.025 g, 0.051 mmol, prepared according to the procedure in Example 1a) to afford the product as the free base (0.010 g, 38%). ^{1}H NMR (300 MHz, d_6-dmso): δ 12.13 (br s, 1H), 8.88 (d, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.40 (s, 1H), 7.60 (d, 1H), 7.45 (d, 1H), 7.06 (d, 1H), 3.69-3.60 (m, 2H), 3.47 (s, 2H), 3.38-3.32 (m, 2H), 3.15 (sept, 1H), 2.96 (tt, 1H), 2.69-2.54 (m, 4H), 2.45-2.38 (m, 2H), 2.37-2.29 (m, 2H), 1.27 (d, 6H); LCMS $(M+H)^+$: 511.4.

Example 25. {trans-3-[4-(piperidin-1-ylcarbonyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



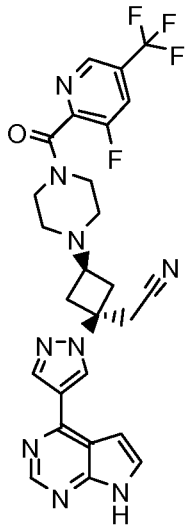
Piperidine (0.020 mL, 0.203 mmol, Aldrich) was dissolved in methylene chloride (0.18 mL) and acetonitrile (0.5 mL), and 1.89 M phosgene in toluene (0.161 mL, 0.304 mmol) was introduced, followed by diisopropylethylamine (0.177 mL, 1.01 mmol). The reaction mixture was stirred for 1 hour, and the solvent and excess phosgene was removed *in vacuo*. N,N-Diisopropylethylamine (0.100 mL, 0.574 mmol) was again added, followed by acetonitrile (0.5 mL). To this solution was added {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.050 g, 0.10 mmol, prepared as in Example 1b, Step 1) in acetonitrile (1 mL). The reaction was stirred overnight and then solvent and excess reagents were removed by evaporation. The crude product was deprotected by stirring with 1:1 TFA:DCM for 2 hours, then evaporation, followed by stirring with excess ethylenediamine in methanol until deprotection was complete. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (0.02 g, 40%). ^{1}H NMR (300 MHz, d_6-dmso): δ 12.12 (br s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, 1H), 7.07 (d, 1H), 3.42 (s, 2H), 3.17-3.05 (m, 8H), 3.04-2.94 (m, 2H), 2.79 (tt, 1H), 2.41-2.24 (m, 6H), 1.57-1.39 (m, 6H); LCMS $(M+H)^+$: 474.1.

Example 26. {cis-3-{4-[4-fluoro-3-(trifluoromethoxy)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

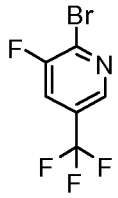


To a mixture of 4-fluoro-3-(trifluoromethoxy)benzoic acid (17.0 mg, 0.0761 mmol, JRD Fluorochem), N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (23.2 mg, 0.0609 mmol) and triethylamine (42.4 μL, 0.304 mmol) in tetrahydrofuran (0.50 mL) that was pre-stirred at room temperature for 15 minutes, was added{cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (25 mg, 0.051 mmol, prepared as in Example 1a). The mixture was stirred for one hour and was diluted with ethyl acetate and water. The mixture was shaken and the layers separated. The organic layer was washed with water, 0.1N NaOH and sat. NaCl solution, dried over sodium sulfate, decanted and concentrated. The residue was dissolved in a 1:1 mixture of DCM:TFA, and stirred for 1 hour. The solvents were removed *in vacuo* and the residue was dissolved in 1 mL methanol and 0.2 ml ethylenediamine. This solution was stirred for one hour. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (0.012 g, 42%). ^1H NMR (300 MHz, d_6-dmso): δ 8.70 (s, 1H), 8.68 (s, 1H), 8.39 (s, 1H), 7.64 (ddd, 1H), 7.60 (d, 1H), 7.59 (dd, 1H), 7.51 (ddd, 1H), 7.05 (d, 1H), 3.61 (br, 2H), 3.47 (s, 2H), 2.95 (tt, 1H), 2.70-2.54 (m, 4H), 2.42-2.22 (m, 4H); LCMS $(M+H)^+$: 569.3.

Example 27. {cis-3-(4-{[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

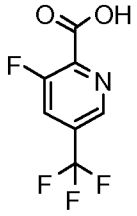


Step 1. 2-bromo-3-fluoro-5-(trifluoromethyl)pyridine



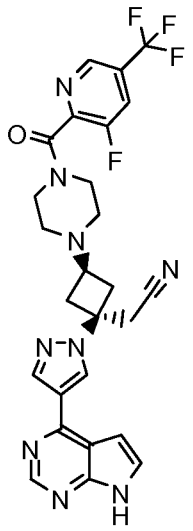
A mixture of 3-fluoro-5-(trifluoromethyl)pyridin-2-ol (1.0 g, 5.5 mmol, Matrix) and phosphoric tribromide (1.6 g, 5.5 mmol) in N,N-dimethylformamide (2.9 mL, 38 mmol) was heated to 130 °C for 70 minutes. After cooling to room temperature, the mixture was poured onto a mixture of ice and sodium bicarbonate solution (final pH=8). The product was extracted with diethyl ether. The extract was washed with water (twice), followed by brine, dried and solvent removed *in vacuo*. Flash chromatography, eluting with a gradient from 0-10% ethyl acetate in hexanes afforded product as a colorless oil (0.59 g, 44%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53-8.50 (m, 1H), 7.66 (dd, 1H).

Step 2. 3-fluoro-5-(trifluoromethyl)pyridine-2-carboxylic acid



2.5 M n-Butyllithium in hexane (1.1 mL, 2.7 mmol) was added to toluene (3.0 mL, 29 mmol) at -75 °C. A solution of 2-bromo-3-fluoro-5-(trifluoromethyl)pyridine (0.59 g, 2.4 mmol, from Step 1) in toluene (0.50 mL) was added. After one hour at -75 °C, CO_2 gas (generated by the evaporation of dry ice in a flask on the side and directed into the reaction flask, sub-surface, via cannula) was bubbled through the solution at -75 °C for 15 minutes, and continued as the reaction warmed to ambient temperature. Solvent was evaporated. The residue was mixed with 4 mL of water, and this aqueous mixture was washed with ether (2x2 ml), and these extracts discarded. The aqueous was then acidifed by the addition of concentrated HCl to pH 1. The resulting light yellow precipitate was collected by filtration (0.30 g, 59%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.78 (s, 1H), 7.93 (d, 1H); LCMS $(M+H)^+$: 210.1.

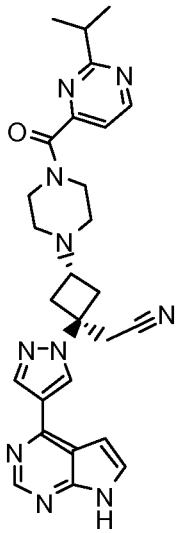
Step 3. {cis-3-(4-{[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



3-Fluoro-5-(trifluoromethyl)pyridine-2-carboxylic acid (16 mg, 0.076 mmol), and {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (25 mg, 0.051 mmol, prepared as described in Example 1a) were coupled, deprotected and purified according to the procedure of Example 26 to afford product as the free base (13 mg, 46%). ^{1}H NMR (400 MHz, d_6-dmso): δ 12.06 (br s, 1H), 8.91 (s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.51 (dd, 1H),

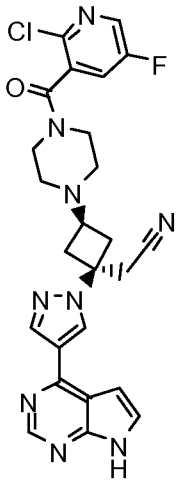
8.39 (s, 1h), 7.60 (d, 1H), 7.06 (d, 1H), 3.74-3.63 (m, 2H), 3.47 (s, 2H), 3.28-3.19 (m, 2H), 2.97 (tt, 1H), 2.70-2.54 (m, 4H), 2.46-2.35 (m, 2H), 2.33-2.21 (m, 2H); LCMS $(M+H)^+$: 554.2.

Example 24b. {trans-3-{4-[(2-isopropylpyrimidin-4-yl)carbonyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



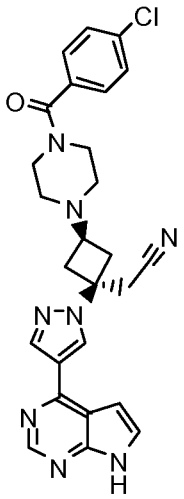
Step 3 of Example 21a was followed, using 2-isopropylpyrimidine-4-carboxylic acid (0.010 g, 0.061 mmol, ChemBridge), and {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.020 g, 0.040 mmol, prepared according to the procedure in Example 1b, Step 1) to afford the product as the free base (0.008 g, 40%). ^{1}H NMR (300 MHz, d_6-dmso): δ 12.13 (br s, 1H), 8.88 (d, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, 1H), 7.45 (d, 1H), 7.07 (d, 1H), 3.72-3.64 (m, 2H), 3.43 (s, 2H), 3.41-3.35 (m, 2H), 3.15 (sept, 1H), 3.07-2.96 (m, 2H), 2.84 (tt, 1H), 2.46-2.29 (m, 6H); LCMS $(M+H)^+$: 511.4.

Example 9a. {cis-3-{4-[(2-chloro-5-fluoropyridin-3-yl)carbonyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



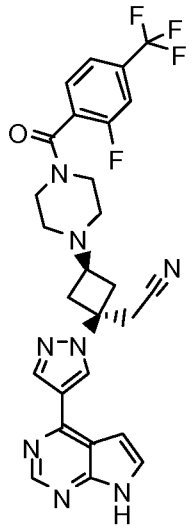
A mixture of 2-chloro-5-fluoronicotinic acid (0.027 g, 0.15 mmol, Matrix), triethylamine (0.041 g, 0.40 mmol) and N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium Hexafluorophosphate (0.046 g, 0.12 mmol, Aldrich) in tetrahydrofuran (0.6 mL) was stirred for 10 minutes, followed by the addition of {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.050 g, 0.10 mmol, prepared as in Example 1a) in tetrahydrofuran (0.6 mL) . Solvent was removed *in vacuo*, the residue was stirred in a solution of 1:1 TFA:DCM for 1 hour, evaporated, and then stirred with 0.2 mL ethylenediamine in methanol until deprotection complete. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (22 mg, 42%). ^1H NMR (300 MHz, d_6-dmso): δ 12.12 (br s, 1H), 8.70 (s, 1H), 8.68 (s, 1h), 8.55 (d, 1H), 8.39 (s, 1H), 8.04 (dd, 1H), 7.60 (d, 1H), 7.06 (d, 1H), 3.77-3.52 (m, 2H), 3.47 (s, 2H), 3.25-3.15 (m, 2H), 2.96 (tt, 1H), 2.75-2.56 (m, 4H), 2.48-2.21 (m, 4H); ^{19}F NMR (282 MHz, d_6-dmso): δ -128.61 (d, 1H); LCMS $(M+H)^+$: 520.1/522.1.

Example 28. {cis-3-{4-[4-chlorobenzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



The procedure of Example 8b was followed, using {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (25 mg, 0.051 mmol, from Example 1a, Step 9) and 4-Chlorobenzoic acid chloride (17.8 mg, 0.101 mmol), to afford product as the free base (15 mg, 59%). ^{1}H NMR (300 MHz, d_6-dmso): δ 12.13 (br s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.39 (s, 1H), 7.60 (s, 1H), 7.53-7.47 (m, 2H), 7.45-7.39 (m, 2H), 7.06 (d, 1H), 3.61 (br, 2H), 3.47 (s, 2H), 3.36-3.23 (br, 2H), 2.95 (tt, 1H), 2.70-2.53 (m, 4H), 2.45-2.20 (m, 4H); LCMS $(M+H)^+$: 501.2/503.2.

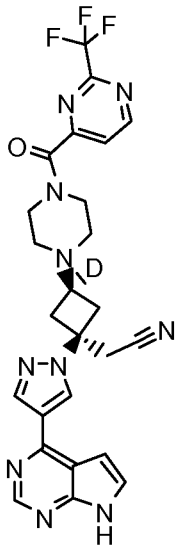
Example 29. {cis-3-{4-[2-fluoro-4-(trifluoromethyl)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile 2.3 x (trifluoroacetate) salt



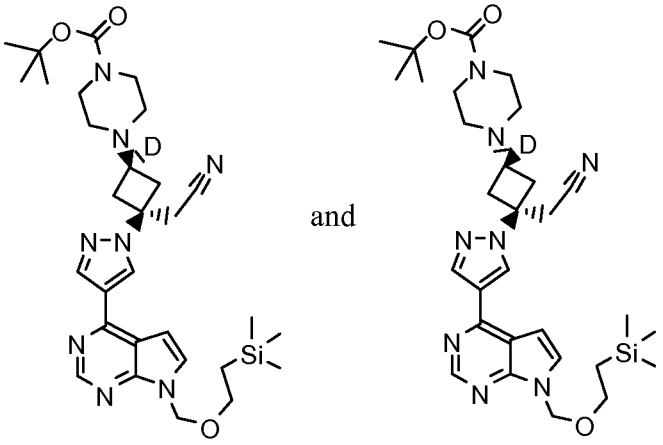
· 2.3 TFA

To a solution of {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.033 g, 0.067 mmol, prepared as in Example 1a) and triethylamine (0.0373 mL, 0.268 mmol) in acetonitrile (0.5 mL) was added 2-fluoro-4-(trifluoromethyl)benzoyl chloride (0.018 g, 0.080 mmol). The reaction was stirred for 2 hours. The reaction mixture was partitioned between 1 N NaOH and ethyl acetate. The organic layer was dried over sodium sulfate, decanted and concentrated. The crude product was deprotected by stirring in a solution of 1:1 DCM: TFA for 1 hour, then evaporation, and stirring with excess ethylenediamine in methanol until deprotection was complete. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.1% TFA). The eluent containing the desired mass was frozen and lyophilized to afford product as the 2.3 x TFA salt. ^{1}H NMR (400 MHz, d_6-dmso): δ 12.35 (s, 1H), 8.80 (s, 1H), 8.70 (s, 1H), 8.42 (s, 1H), 7.81 (d, 1H), 7.72-7.65 (m, 2H), 7.64 (dd, 1H), 7.07 (dd, 1H), 3.91-2.73 (br m, 15H); ^{19}F NMR (376 MHz, d_6-dmso): δ -61.77 (s, 3F), -74.60 (s, 6.9 F), -113.98 (br s, 1F); LCMS $(M+H)^+$: 553.2.

Example 30. [cis-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile-d1



Step 1. tert-butyl 4-{cis-3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazine-1-carboxylate-d1 and tert-butyl 4-{trans-3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazine-1-carboxylate-d1



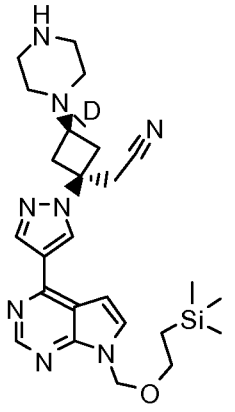
Sodium cyano(trihydrido)borate(1-)-d3 (0.02 g, 0.2 mmol, Aldrich) and zinc dichloride (0.02 g, 0.1 mmol) were precombined in a small quantity of methanol and were stirred for 2 hours. {3-oxo-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.100 g, 0.237 mmol, Example 1a, Step 7) and tert-butyl piperazine-1-carboxylate (0.0882 g, 0.473

mmol) were combined in methanol (4 mL, 100 mmol) and stirred for 15 minutes to dissolve. The mixture of sodium cyano(trihydrido)borate(1-)-d3 and zinc dichloride was then added. The reaction was continued for 4 hours. Methanol was removed *in vacuo*. The residue was reconstituted in ethyl acetate, and this solution was washed with saturated sodium bicarbonate solution. The aqueous basic solution was extracted with five further portions of ethyl acetate, which were combined with the original organic layer. The combined extracts were dried over sodium sulfate, filtered and concentrated. The cis and trans isomers were separated by chiral HPLC (Chiralcel OJ-H, 20 x 250 mm, 5 u packing, 30% EtOH/70% Hexanes at a flow rate of 12 mL/min). Peak 1, cis-: retention time 10.58 minutes, 55 mg (39%). Peak 2, trans-: retention time 14.95 minutes, 51 mg (36%).

^{1}H NMR peak 1, cis, (300 MHz, $CDCl_3$): δ 8.83 (s, 1H), 8.37 (s, 1H), 8.28 (s, 1H), 7.39 (d, 1H), 6.79 (d, 1H), 5.66 (s, 2H), 3.53 (dd, 2H), 3.45-3.38 (m, 4H), 3.12 (s, 2H), 2.78 (d, 2H), 2.67 (d, 2H), 2.35-2.26 (m, 4H), 1.45 (s, 9H), 0.91 (dd, 2H), -0.07 (s, 9H); LCMS $(M+H)^+$: 594.1.

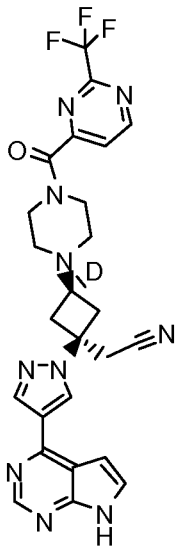
^{1}H NMR peak 2, trans, (300 MHz, $CDCl_3$): δ 8.84 (s, 1H), 8.46 (s, 1H), 8.32 (s, 1H), 7.40 (d, 1H), 6.81 (d, 1H), 5.67 (s, 2H), 3.54 (dd, 2H), 3.50-3.43 (m, 4H), 3.21 (s, 2H), 3.02 (d, 2H), 2.51 (d, 2H), 2.40-2.31 (m, 4H), 1.45 (s, 9H), 0.91 (dd, 2H), -0.07 (s, 9H); LCMS $(M+H)^+$: 594.0.

Step 2. {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile-d1



To a solution of tert-butyl 4-{cis-3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazine-1-carboxylate-d1 (0.083 g, 0.14 mmol, Peak 1, prepared according to the method of Step 1) in 1,4-dioxane (5 mL) was added 4.0 M hydrogen chloride in water (0.7 mL, 3 mmol), and the deprotection reaction was stirred over two nights. The reaction mixture was then poured into sufficient saturated sodium bicarbonate solution to make the mixture basic, and this was extracted with ethyl acetate three times. The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated, to afford product, which was used without further purification (0.07 g, 100%). LCMS $(M+H)^+$: 494.0.

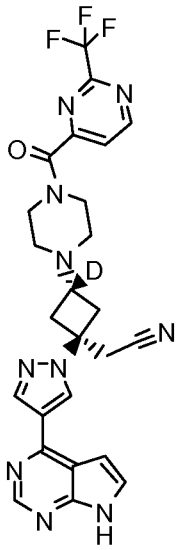
Step 3 of Example 30. [cis-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile-d1



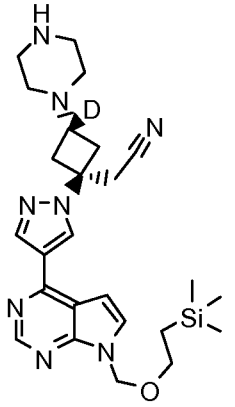
A mixture of 2-(trifluoromethyl)pyrimidine-4-carboxylic acid (0.049 g, 0.25 mmol, prepared by hydrolysis of the ester available from Apollo as described in WO2006/067445), N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.085 g, 0.22 mmol, Aldrich), and triethylamine (0.10 mL, 0.75 mmol) in tetrahydrofuran (1 mL) was prestirred for 5 minutes, followed by the addition of {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-

d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile-d1 (0.07 g, 0.15 mmol, from Step 2) in tetrahydrofuran (4 mL). The reaction was stirred overnight. The THF was removed *in vacuo*, and the residue was partitioned between saturated sodium bicarbonate solution and ethyl acetate. The layers were separated and the aqueous was extracted with two further portions of ethyl acetate. The combined extracts were dried over sodium sulfate, decanted and concentrated. Flash chromatography, eluting with a gradient from 0-10% MeOH in DCM was used to purify the SEM-protected intermediate. This product was stirred with trifluoroacetic acid (2 mL) in methylene chloride (2 mL) for 2 hours. The solvents were removed *in vacuo*. The residue was reconstituted in methanol (4 mL) and ethylenediamine (0.2 mL, 3 mmol) was added. The second step of the deprotection was continued overnight. The reaction was worked up by partition between water and ethyl acetate, and the aqueous portion was extracted with ethyl acetate a total of three times. The combined extracts were dried over sodium sulfate, filtered and concentrated. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (0.010 g, 12%). ^{1}H NMR (300 MHz, CD_3OD): δ 9.13 (d, 1H), 8.66 (s, 1H), 8.63 (s, 1H), 8.37 (s, 1H), 7.88 (d, 1H), 7.51 (d, 1H), 6.98 (d, 1H), 3.82 (dd, 2H), 3.53 (dd, 2H), 3.34 (s, 2H), 2.81 (dd, 2H), 2.69 (dd, 2H), 2.57 (dd, 2H), 2.49 (dd, 2H); ^{19}F NMR (282 MHz, CD_3OD): δ -72.46 (s, 3F); LCMS $(M+H)^+$: 537.8.

Example 31. [trans-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile-d1

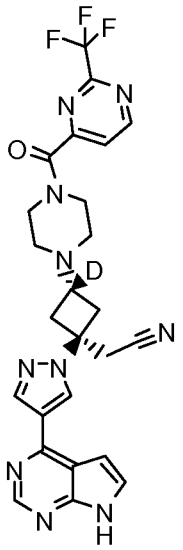


Step 1. {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile-d1



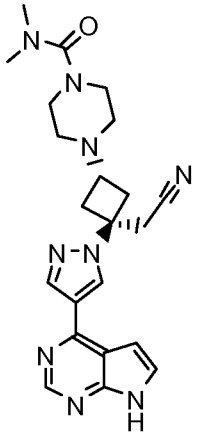
The procedure of Example 30, Step 2 was followed, using Peak 2 produced in Example 30, Step 1: tert-butyl 4-{trans-3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazine-1-carboxylate-d1 (0.076 g, 0.13 mmol) to afford the trans-product, which was used without further purification (47 mg, 74%). LCMS $(M+H)^+$: 494.0.

Step 2. [trans-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile-d1



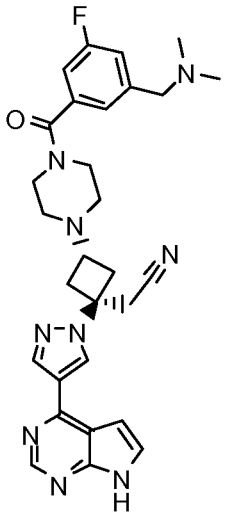
The product of Step 1, {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile-d1 (0.047 g, 0.095 mmol), was coupled with 2-(trifluoromethyl)pyrimidine-4-carboxylic acid (0.046 g, 0.24 mmol, prepared by hydrolysis of the ester available from Apollo as described in WO2006/067445) according to the procedure of Example 30, Step 3 (10 mg, 20%). ^{1}H NMR (300 MHz, CD_3OD): δ 9.13 (d, 1H), 8.71 (s, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.88 (d, 1H), 7.51 (d, 1H), 6.98 (d, 1H), 3.94-3.79 (m, 2H), 3.64-3.50 (m, 2H), 3.34 (s, 2H), 3.07 (d, 2H), 2.64-2.43 (m, 6H); ^{19}F NMR (282 MHz, CD_3OD): δ -72.45 (s, 3F); LCMS $(M+H)^+$: 537.8.

Example 32. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N,N-dimethylpiperazine-1-carboxamide

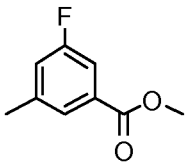


{trans-3-Piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, from Example 1b, Step 1) was dissolved in acetonitrile (1 mL) and Methylene chloride (0.5 mL). N,N-Diisopropylethylamine (0.10 mL, 0.57 mmol) followed by N,N-Dimethylcarbamoyl chloride (25 μL, 0.27 mmol, Aldrich) were added. After a reaction time of 1.5 hours, solvent was removed *in vacuo*. The crude product was stirred with 1:1 TFA:DCM for 2 hours, then evaporated and stirred with excess ethylenediamine (0.2 mL) in methanol until deprotection was complete. The product was purified via preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford product as the free base (0.012 g, 45%). ^1H NMR (300 MHz, d_6-dmso): δ 12.10 (s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.41 (s, 1H), 7.60 (d, 1H), 7.07 (d, 1H), 3.42 (s, 2H), 3.16-3.07 (m, 4H), 3.05-2.94 (m, 2H), 2.78 (tt, 1H), 2.71 (s, 6H), 2.40-2.24 (m, 6H); LCMS $(M+H)^+$: 434.2.

Example 33. {trans-3-(4-{3-[(dimethylamino)methyl]-5-fluorobenzoyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

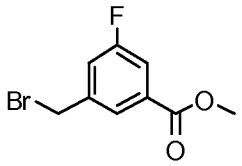


Step 1. methyl 3-fluoro-5-methylbenzoate



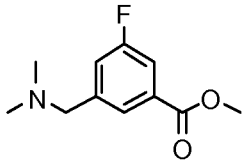
To a solution of 3-fluoro-5-methylbenzoic acid (1.50 g, 9.73 mmol, Oakwood) in Acetone (40 mL) was added Potassium carbonate (1.34 g, 9.73 mmol) followed by Methyl iodide (0.73 mL, 12 mmol) . The reaction mixture was heated to 65 °C for 1 hour, heating discontinued and stirred overnight, then heating resumed at that temperature for a further 2 hours. Additional Methyl iodide (0.5 mL, 8 mmol) was added and heating was continued for 6 hours. Solids were removed by filtration and acetone was removed *in vacuo*. The residue was partitioned between 1N NaOH and ethyl acetate. The aqueous portion was extracted with a further two portions of ethyl acetate. The combined extracts were washed with brine, then dried over sodium sulfate, decanted and concentrated. The product so obtained was used without further purification (1.64 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66-7.63 (m, 1H), 7.51 (d, 1H), 7.10-7.04 (m, 1H), 3.91 (s, 3H), 2.40 (s, 3H).

Step 2. methyl 3-(bromomethyl)-5-fluorobenzoate



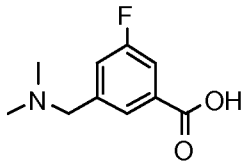
To a solution of methyl 3-fluoro-5-methylbenzoate (1.64 g, 9.75 mmol, from Step 1) and N-bromosuccinimide (2.05 g, 11.5 mmol) in carbon tetrachloride (20 mL) was added benzoyl peroxide (0.1 g, 0.6 mmol) and the mixture was heated to reflux for four hours. The reaction was then cooled to room temperature, filtered, and diluted with DCM. The solution was washed successively with sodium thiosulfate, 1N NaOH, water, and brine, dried over sodium sulfate, decanted and concentrated. Flash chromatography, eluting with a gradient from 0-20% ethyl acetate in hexanes, afforded a partially purified product. The cleanest fractions were used in the displacement with amine in Step 3. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87-7.85 (m, 1H), 7.68-7.62 (m, 1H), 7.31 (ddd, 1H), 4.47 (s, 2H), 3.93 (s, 3H).

Step 3. methyl 3-[(dimethylamino)methyl]-5-fluorobenzoate



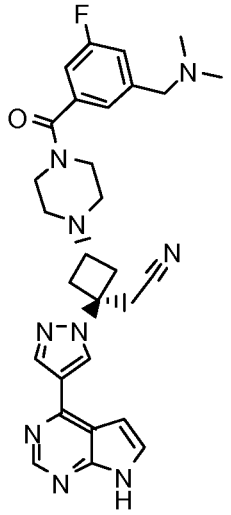
To a solution of 2.0 M dimethylamine in THF (3.24 mL, 6.48 mmol) was added methylene chloride (2 mL) and methyl 3-(bromomethyl)-5-fluorobenzoate (0.200 g, 0.810 mmol from Step 2). The reaction was heated in a sealed reaction vessel in an oil bath held at 60 °C for 2 hours. Solvent and excess reagent were removed *in vacuo* and the residue was subjected to flash chromatography, eluting with a gradient from 0-20% MeOH in DCM containing some NH_4OH (50 mg, 29%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80-7.77 (m, 1H), 7.62 (ddd, 1H), 7.29 (ddd, 1H), 3.90 (s, 3H), 3.53 (s, 2H), 2.29 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$): δ -113.10 (t, 1F); LCMS $(M+H)^+$: 212.1.

Step 4. 3-[(dimethylamino)methyl]-5-fluorobenzoic acid



Methyl 3-[(dimethylamino)methyl]-5-fluorobenzoate (0.040 g, 0.19 mmol from Step 3) was dissolved in tetrahydrofuran (3 mL) and lithium hydroxide monohydrate (0.0954 g, 2.27 mmol) dissolved in water (1 mL) was added. The reaction was stirred for 3 hours. The crude reaction mixture was purified by preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was evaporated using rotary evaporation to afford product (22 mg, 59%), which was used directly in Step 5. LCMS $(M+H)^+$: 198.1.

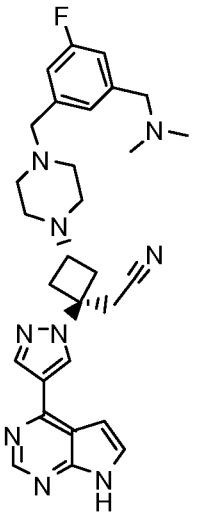
Step 5. {trans-3-(4-{3-[(dimethylamino)methyl]-5-fluorobenzoyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



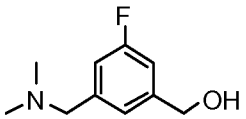
To a mixture of 3-[(dimethylamino)methyl]-5-fluorobenzoic acid (0.018 g, 0.091 mmol, from Step 4) in N,N-dimethylformamide (1.5 mL, 19 mmol) and triethylamine (0.06 mL, 0.4 mmol) was added N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.028 g, 0.073 mmol). After stirring for 5 minutes, {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, from Example 1b, Step 1) in tetrahydrofuran (1.5 mL, 18 mmol) was

added, and the reaction was stirred for 3 hours. Saturated sodium bicarbonate solution was added, and the product was extracted with three portions of ethyl acetate. The combined extracts were dried over sodium sulfate, decanted and concentrated. The residue was stirred with 1:1 TFA:DCM for 1 hour, evaporated, and then stirred with 0.2 mL ethylenediamine in methanol until deprotection was complete. The product was purified by preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford the product as the free base (15 mg, 45%). ^{1}H NMR (500 MHz, CD_3OD): δ 8.69 (s, 1H), 8.66 (s, 1H), 8.38 (s, 1H), 7.49 (d, 1H), 7.22-7.19 (m, 1H), 7.18 (s, 1H), 7.09 (ddd, 1H), 6.96 (d, 1H), 3.87-3.72 (br s, 2H), 3.51 (s, 2H), 3.52-3.43 (br s, 2H), 3.33 (s, 2H), 3.10-3.03 (m, 2H) 2.95 (tt, 1H), 2.55-2.34 (m, 6H), 2.24 (s, 6H); ^{19}F NMR (282 MHz, d_6-dmso): δ -113.45 (dd, 1F); LCMS $(M+H)^+$: 542.3.

Example 34. {trans-3-(4-{3-[(dimethylamino)methyl]-5-fluorobenzyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



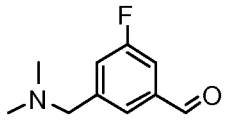
Step 1. {3-[(dimethylamino)methyl]-5-fluorophenyl}methanol



To a solution of methyl 3-[(dimethylamino)methyl]-5-fluorobenzoate (0.14 g,

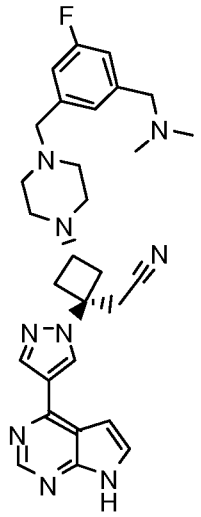
0.66 mmol, Example 33, Step 3) in Ether (4 mL) at 0 °C in an ice bath was added dropwise 1.0 M lithium tetrahydroaluminate in THF (1.32 mL, 1.32 mmol). The reaction was allowed to warm to room temperature and stirred for 1.5 hours. The reaction mixture was re-cooled in an ice bath and methanol, followed by 1 N NaOH, were added to quench the reaction. The product was extracted from the reaction mixture with three portions of ethyl acetate. The combined extracts were dried over sodium sulfate, decanted and concentrated, to afford product which was used without further purification (0.100 g, 82%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.13-6.94 (m, 3H), 4.59 (s, 2H), 3.47 (s, 2H), 2.24 (s, 6H); ^{19}F NMR (282 MHz, CD_3OD): δ -116.41 (t, 1F); LCMS $(M+H)^+$: 184.0.

Step 2. 3-[(dimethylamino)methyl]-5-fluorobenzaldehyde



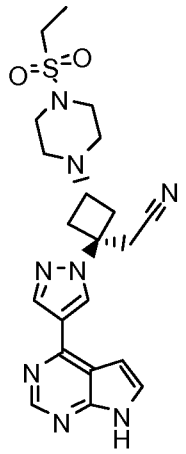
To a solution of {3-[(dimethylamino)methyl]-5-fluorophenyl}methanol (0.100 g, 0.546 mmol, from Step 1) in Chloroform (3 mL) was added manganese(IV) oxide (0.145 g, 1.42 mmol) and the mixture was heated in an oil bath held at 80 °C for 7 hours. The reaction mixture was filtered, rinsing with copious $CHCl_3$ and the solvent was removed from the filtrate *in vacuo*. The product of the reaction, containing approximately 50% aldehyde and 50% unreacted alcohol was used without further purification in Step 3. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.99 (d, 1H), 7.78 (dd, 1H), 7.67 (ddd, 1H), 7.52 (ddd, 1H), 4.28 (s, 2H), 2.84 (s, 6H); LCMS $(M+H)^+$: 182.0.

Step 3. {trans-3-(4-{3-[(dimethylamino)methyl]-5-fluorobenzyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



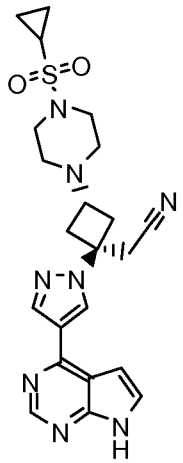
A solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, Example 1b, Step 1) and 3-[(dimethylamino)methyl]-5-fluorobenzaldehyde (0.022 g, 0.12 mmol, from Step 2) in methylene chloride (1 mL, 20 mmol) was treated with sodium triacetoxyborohydride (0.0645 g, 0.304 mmol) and stirred overnight. Solvent was removed *in vacuo*. The SEM-protected intermediate was reconstituted in methanol and purified by preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass subjected to rotary evaporation to remove solvent. To deprotect, the product was stirred with 1:1 TFA:DCM for 1 hour, evaporated, and then stirred with 0.2 mL ethylenediamine in methanol for 30 minutes. The deprotected product was purified by preparative HPLC-MS (C18, eluting with a gradient of H_2O/MeCN containing 0.15% NH_4OH). The eluent containing the desired mass was frozen and lyophilized to afford the product as the free base (8 mg, 20%). ^{1}H NMR (500 MHz, CD_3OD): δ 8.69 (s, 1H), 8.66 (s, 1H), 8.38 (s, 1H), 7.49 (d, 1H), 7.10 (s, 1H), 7.02 (ddd, 1H), 6.98 (ddd, 1H), 6.96 (d, 1H), 3.55 (s, 2H), 3.46 (s, 2H), 3.31 (s, 2H), 3.08-3.01 (m, 2H), 2.93 (tt, 1H), 2.61-2.40 (m, 10H), 2.23 (s, 6H); ^{19}F NMR (282 MHz, d_6-dmso): δ -115.07 (t, 1F); LCMS $(M+H)^+$: 528.3.

Example 35. {trans-3-[4-(ethylsulfonyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



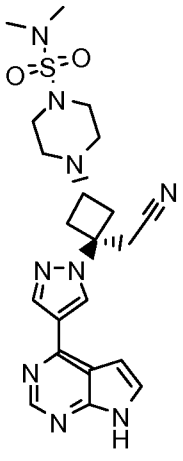
{trans-3-Piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (30.0 mg, 0.061 mmol, prepared as in Example 1b, Step 1) was dissolved in methylene chloride (0.50 mL) , then triethylamine (17 μL, 0.12 mmol) and ethanesulfonyl chloride (7.5 μL, 0.079 mmol) were added. The reaction was stirred for1 hour, and the mixture was concentrated. The residue was stirred in 1:1 TFA/DCM for 1 hour, then was concentrated, dissolved in 1 mL methanol, and 0.2 mL ethylenediamine was added. Purification via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) followed by lyophilization afforded the product as the free base (15 mg, 54%). ^1H NMR (400 MHz, d_6-dmso): δ 12.10 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, 1H), 7.07 (d, 1H), 3.42 (s, 2H), 3.23-3.16 (m, 4H), 3.06 (q, 2H), 3.06-2.96 (m, 2H), 2.84 (tt, 1H), 2.43-2.29 (m, 6H), 1.21 (t, 3H); LCMS $(M+H)^+$: 455.3.

Example 36. {trans-3-[4-(cyclopropylsulfonyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



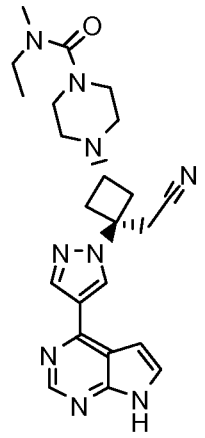
The compound was prepared as in Example 35, using cyclopropanesulfonyl chloride (8.1 μL, 0.079 mmol). (10.2 mg, 36%). ^{1}H NMR (400 MHz, d_6-dmso): δ 12.12 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, 1H), 7.07 (d, 1H), 3.42 (s, 2H), 3.26-3.16 (m, 4H), 3.06-2.97 (m, 2H), 2.84 (tt, 1H), 2.61 (tt, 1H), 2.44-2.30 (m, 6H), 1.03-0.88 (m, 4H); LCMS $(M+H)^+$: 467.1.

Example 37. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N,N-dimethylpiperazine-1-sulfonamide



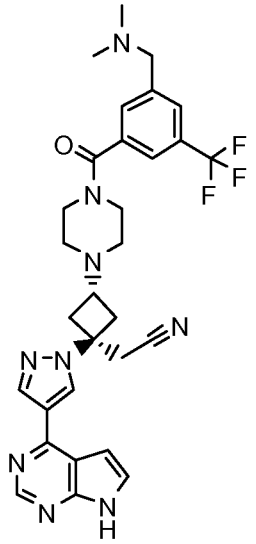
The compound was prepared as in Example 35, using dimethylsulfamoyl chloride (8.5 μL, 0.079 mmol). (13 mg, 45%). ^{1}H NMR (400 MHz, d_6-dmso): δ 12.12 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, 1H), 7.07 (d, 1H), 3.42 (s, 2H), 3.21-3.15 (m, 4H), 3.05-2.96 (m, 2H), 2.83 (tt, 1H), 2.76 (s, 6H), 2.40-2.29 (m, 6H); LCMS $(M+H)^+$: 470.0.

Example 38. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-ethyl-N-methylpiperazine-1-carboxamide



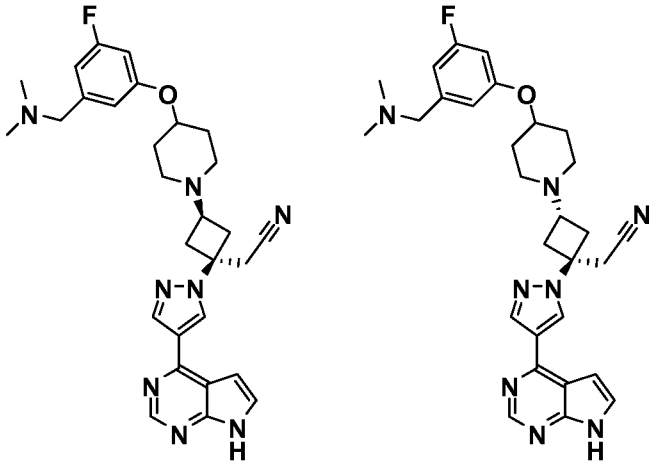
{trans-3-Piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, prepared as in Example 1b, Step 1) was dissolved in methylene chloride (0.50 mL), and Triethylamine (0.0339 mL, 0.244 mmol) and ethyl(methyl)carbamic chloride (14.8 mg, 0.122 mmol, Toronto Research Chemicals) were added. The reaction mixture was stirred for 2 hours, and solvent was removed *in vacuo*. The residue was stirred with 1:1 TFA:DCM for 1 hour, then evaporated and stirred with 0.2 mL ethylenediamine in methanol until the deprotection was complete. Purification via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) followed by lyophilization afforded the product as the free base (15.4 mg, 56%). ^{1}H NMR (400 MHz, d_6-dmso): δ 12.08 (br s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, 1H), 7.07 (d, 1H), 3.42 (s, 2H), 3.14-3.05 (m, 6H), 3.04-2.95 (m, 2H), 2.78 (tt, 1H), 2.70 (s, 3H), 2.40-2.25 (m, 6H), 1.03 (t, 3H); LCMS $(M+H)^+$: 448.2.

Example 39. {trans-3-{4-[3-[(dimethylamino)methyl]-5-(trifluoromethyl)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Lithium 3-[(dimethylamino)methyl]-5-(trifluoromethyl)benzoate (23.1 mg, 0.0913 mmol, US 2010/197924) was dissolved in tetrahydrofuran (0.67 mL), triethylamine (33.9 μL, 0.244 mmol) and N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (32.4 mg, 0.0852 mmol) were added, and after stirring for 15 minutes, {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (30.0 mg, 0.0609 mmol, prepared as in Example 1b, Step 1) was added. The reaction was continued for 2 hours. The reaction mixture was diluted with ethyl acetate and water, shaken, and the layers separated. The organic layer was washed with water, 0.1N NaOH and saturated NaCl solution, dried over sodium sulfate and concentrated. The residue was dissolved in a 1:1 mixture of DCM:TFA, stirred for 1 hour, and solvents were removed *in vacuo*. The residue was dissolved in 1 mL methanol, and 0.2 mL of ethylenediamine was added. The reaction was stirred until deprotection was complete. Purification via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) followed by lyophilization afforded the product as the free base (20 mg, 56%). ^1H NMR (400 MHz, d_6-dmso): δ 12.08 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.71 (s, 1H), 7.62 (s, 1H), 7.60 (d, 1H), 7.59 (s, 1H), 7.07 (d, 1H), 3.67 (br s, 2H), 3.51 (s, 2H), 3.43 (s, 2H), 3.40-3.27 (m, 4H), 3.05-2.96 (m, 2H), 2.84 (tt, 1H), 2.46-2.23 (m, 6H), 2.15 (s, 6H); ^{19}F NMR (376 MHz, d_6-dmso): δ -61.48 (s, 3F); LCMS $(M+H)^+$: 592.3.

Example 40. {cis-3-(4-{3-[(dimethylamino)methyl]-5-fluorophenoxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile; and {trans-3-(4-{3-[(dimethylamino)methyl]-5-fluorophenoxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step 1. (3-{[tert-butyl(diphenyl)silyl]oxy}cyclobutylidene)acetonitrile

To a solution of 1.0 M potassium tert-butoxide in tetrahydrofuran (5.95 mL, 5.95 mmol) at 0 °C was added diethyl cyanomethylphosphonate (1.05 g, 5.95 mmol). The bath was removed and reaction allowed to warm to room temperature for 1 hour. The reaction was cooled to 0 °C and a solution of 3-{[*tert*-butyl(diphenyl)silyl]oxy}cyclobutanone (1.95 g, 6.01 mmol) in THF (10 mL) was added. Upon complete addition, the bath was removed and the reaction was allowed to warm to room temperature and stir overnight. The reaction solution was diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate three times. The combined extracts were washed with brine, dried over sodium sulfate, decanted and concentrated. The crude was purified silica gel column to give the desired product (2.07 g, 90%) as an oil. LCMS $(M+H)^+$: 348.2.

Step 2. {3-{[tert-butyl(diphenyl)silyl]oxy}-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

To a solution of (3-{[*tert*-butyl(diphenyl)silyl]oxy}cyclobutylidene)acetonitrile (1.859 g, 4.065 mmol) and 4-(1H-pyrazol-4-yl)-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine (1.28 g, 4.06 mmol) in acetonitrile (10 mL) was added 1,8-

diazabicyclo[5.4.0]undec-7-ene (0.61 mL, 4.1 mmol). The reaction was stirred overnight. The solvent was remove *in vacuo*. The crude was purified with silica gel column to give of the product (2.7 g, 79%) as an oil. LCMS $(M+H)^+$: 663.3.

Step 3. {3-hydroxy-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

To {3-{[*tert*-butyl(diphenyl)silyl]oxy}-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (2.85 g, 4.30 mmol) in ethanol (120 mL) was added 5.0 M sodium hydroxide in water (29 mL, 150 mmol). The reaction was stirred for 3 hours and diluted with water. The ethanol was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate three times. The combine organic solutions were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified with silica gel column eluting with a gradient from 0-10% MeOH/DCM.to give of the product (1.62 g, 88%) as .off-white foam. LCMS $(M+H)^+$: 425.2.

Step 4. {3-oxo-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

To a solution of {3-hydroxy-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (1.62 g, 3.82 mmol) in DCM (50 mL) at 0 °C was added Dess-Martin periodinane (2.1 g, 5.0 mmol). After stirring for 2 hours, the reaction solution was diluted with ether and saturated $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate three times. The combined extracts were washed with brine, dried over sodium sulfate, decanted and evaporated. The crude was used in the next step without purification. LCMS $(M+H)^+$: 423.2.

Step 5. tert-butyl 4-(3-bromo-5-fluorophenoxy)piperidine-1-carboxylate

To a mixture of triphenylphosphine (1.75 g, 6.66 mmol) and 3-bromo-5-fluorophenol (795 mg, 4.16 mmol) and *tert*-butyl 4-hydroxypiperidine-1-carboxylate

(922 mg, 4.58 mmol) in THF (20. mL) was added di-*tert*-butyl azodicarboxylate (1.53 g, 6.66 mmol) (DBAD) at 0°C. The reaction was stirred overnight at room temperature. The solvent was removed and the residue was dissolved in methanol and purified by preparative-LCMS (C18 column eluting with a gradient of ACN/H_2O containing 0.15% NH_4OH) to give the desired product (1.09 g, 70%). LCMS $(M+Na)^+$: 396.0, 398.0.

Step 6. tert-butyl 4-{3-[(dimethylamino)methyl]-5-fluorophenoxy}piperidine-1-carboxylate

To a microwave vial was added *tert*-butyl 4-(3-bromo-5-fluorophenoxy)piperidine-1-carboxylate (215 mg, 0.574 mmol), cesium carbonate (562 mg, 1.72 mmol), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (130 mg, 0.27 mmol), potassium [(dimethylamino)methyl](trifluoro)borate(1-) (114 mg, 0.689 mmol), palladium acetate (30.7 mg, 0.137 mmol) and 5.05 M water in THF (3.5 mL). The tube was sealed and evacuated and refilled with N_2 (3×). The sealed tube was then heated at 80 °C for 20 hours. The reaction was diluted with water and ethyl acetate. The aqueous layer was extracted with ethyl acetate once. The combined organic solutions were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified with preparative LCMS (C18 column eluting with a gradient of ACN/H_2O containing 0.1% TFA) to afford the desired product (180 mg, 89%). LCMS $(M+H)^+$: 353.2.

Step 7. 1-[3-fluoro-5-(piperidin-4-yloxy)phenyl]-N,N-dimethylmethanamine dihydrochloride

To a solution of *tert*-butyl 4-{3-[(dimethylamino)methyl]-5-fluorophenoxy}piperidine-1-carboxylate (180 mg, 0.51 mmol) in DCM (2.4 mL) was added 4.0 M hydrogen chloride in dioxane (1.0 mL, 4.1 mmol). The reaction solution was stirred at room temperature for 6 hours. The solvent was removed to give the desired product as white solid (145 mg, 87%). LCMS $(M+H)^+$: 253.1.

Step 8. {cis-3-(4-{3-[(dimethylamino)methyl]-5-fluorophenoxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-

yl]cyclobutyl}acetonitrile; and {trans-3-(4-{3-[(dimethylamino)methyl]-5-fluorophenoxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

To a solution of zinc dichloride (14.8 mg, 0.109 mmol) in methanol (2 mL) was added sodium cyanoborohydride (13.7 mg, 0.218 mmol). After stirring for 2 hours, a solution of {3-oxo-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (91.9 mg, 0.217 mmol) and 1-[3-fluoro-5-(piperidin-4-yloxy)phenyl]-*N*,*N*-dimethylmethanamine (78 mg, 0.31 mmol) in methanol (0.50 mL) was added to reaction vial. The resulting mixture was stirred overnight at room temperature. The mixture was diluted with methanol and purified with prep-LCMS (C18 column eluting with a gradient of ACN/H_2O containing 0.15% NH_4OH) to give two isomers.

Isomer 1 (first to elute): LCMS $(M+H)^+$: 659.4.

Isomer 2 (second to elute): LCMS $(M+H)^+$: 659.4.

Step 9. {cis-3-(4-{3-[(dimethylamino)methyl]-5-fluorophenoxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile; and {trans-3-(4-{3-[(dimethylamino)methyl]-5-fluorophenoxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

To a solution of {cis-3-(4-{3-[(dimethylamino)methyl]-5-fluorophenoxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (isomer 1 from last step) (23.1 mg, 0.0350 mmol) in DCM (0.5 mL) was added trifluoroacetic acid (0.5 mL). The reaction solution was stirred for 1 h. The solvent was then removed and residue was dissolved in methanol (1.0 mL) and ethylenediamine (100. μL, 1.50 mmol) was added. The reaction solution was stirred for 2 h and diluted with methanol and purified with prep-LCMS (C18 column eluting with a gradient of ACN/H_2O containing 0.15% NH_4OH) to give the desired product as white solid.

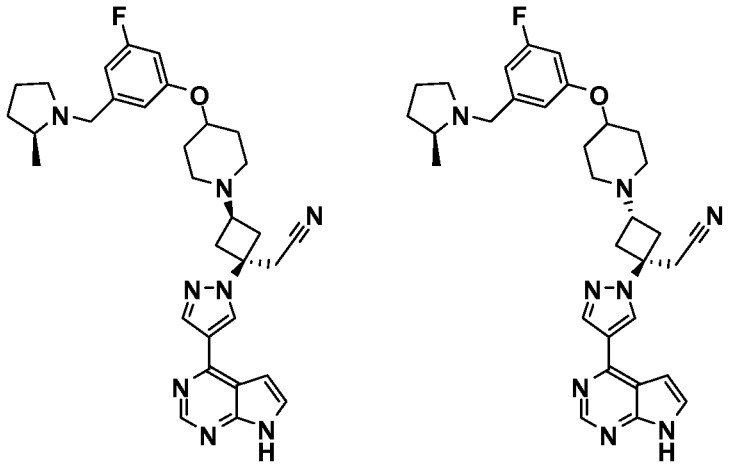
Isomer 1 (first to elute): ^1H NMR (400 MHz, CD_3OD): δ 8.67 (d, 1H), 8.66 (s, 1H), 8.37 (s, 1H), 7.51 (d, 1H), 7.00 (d, 1H), 6.74 (s, 1H), 6.63 (m, 2H), 4.46 (m, 1H),

3.42 (s, 2H), 3.35 (s, 2H), 3.00 (m, 1H), 2.85-2.66 (m, 6H), 2.36 (m, 2H), 2.23 (s, 6H), 2.04 (m, 2H), 1.81 (m, 2H); LCMS $(M+H)^+$: 529.3.

Trans isomer was prepared in same manner, using {trans-3-(4-{3-[(dimethylamino)methyl]-5-fluorophenoxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (isomer 2 from last step) as starting material.

Isomer 2 (second to elute): ^{1}H NMR (400 MHz, CD_3OD): δ 8.74 (s, 1H), 8.67 (s, 1H), 8.41 (s, 1H), 7.51 (d, 1H), 6.99 (d, 1H), 6.73 (s, 1H), 6.63 (m, 2H), 4.44 (m, 1H), 3.41 (s, 2H), 3.31 (s, 2H), 3.10 (m, 2H), 2.95 (m, 1H), 2.71 (m, 2H), 2.47 (m, 2H), 2.31 (m, 2H), 2.23 (s, 6H), 2.04 (m, 2H), 1.80 (m, 2H); LCMS $(M+H)^+$: 529.3.

Example 41. {cis-3-[4-(3-fluoro-5-{[(2S)-2-methylpyrrolidin-1-yl]methyl}phenoxy)piperidin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile; and {trans-3-[4-(3-fluoro-5-{[(2S)-2-methylpyrrolidin-1-yl]methyl}phenoxy)piperidin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step 1. tert-butyl 4-(3-fluoro-5-formylphenoxy)piperidine-1-carboxylate

To a solution of *tert*-butyl 4-(3-bromo-5-fluorophenoxy)piperidine-1-carboxylate (0.666 g, 1.78 mmol) in THF (9.0 mL) at -78 °C was added 2.5 M n-butyllithium in hexane (0.78 mL, 2.0 mmol). The solution was stirred at same temperature for 30 minutes, then *N,N*-dimethylformamide (1.4 mL, 18 mmol) was added to reaction flask.

The reaction solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water, and aqueous layer was extracted with ethyl acetate twice. The combined organic solutions were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was diluted with methanol and purified with prep-LCMS (C18 column eluting with a gradient of ACN/H_2O containing 0.15% NH_4OH) to give the desired product as an oil (75 mg, 13%). LCMS $(M+H-100)^+$: 224.1.

Step 2. tert-butyl 4-(3-fluoro-5-{[(2S)-2-methylpyrrolidin-1-yl]methyl}phenoxy)piperidine-1-carboxylate trifluoroacetate

To a mixture of (2*S*)-2-methylpyrrolidine (30. μL, 0.30 mmol) and *tert*-butyl 4-(3-fluoro-5-formylphenoxy)piperidine-1-carboxylate (90.0 mg, 0.278 mmol) in DCM (1.3 mL) was added resin of sodium triacetoxyborohydride (13 mg, 0.032 mmol). The resulting mixture was stirred overnight. The reaction mixture was filtered, washing with additional DCM, and concentrated. The residue was purified by preparative-LCMS (C18 column eluting with a gradient of acetonitrile (ACN)/H_2O containing 0.1% trifluoroacetic acid (TFA)) to give the desired product (98 mg, 70%). LCMS $(M+H)^+$: 393.2.

Step 3.(3-fluoro-5-{[(2S)-2-methylpyrrolidin-1-yl]methyl}phenoxy)piperidine

This compound was prepared according to the method of Example 40, Step 7 using *tert*-butyl 4-(3-fluoro-5-{[(2*S*)-2-methylpyrrolidin-1-yl]methyl}phenoxy)piperidine-1-carboxylate trifluoroacetate as starting material. LCMS $(M+H)^+$: 293.1.

Step 4. {cis-3-[4-(3-fluoro-5-{[(2S)-2-methylpyrrolidin-1-yl]methyl}phenoxy)piperidin-1-yl]-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile; and {trans-3-[4-(3-fluoro-5-{[(2S)-2-methylpyrrolidin-1-yl]methyl}phenoxy)piperidin-1-yl]-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

These compounds were prepared according to the method of Example 40, Step 8 using (3-fluoro-5-{[(2*S*)-2-methylpyrrolidin-1-yl]methyl}phenoxy)piperidine as starting material. LCMS $(M+H)^+$: 699.5.

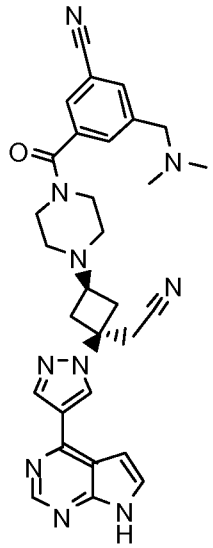
Step 5. {cis-3-[4-(3-fluoro-5-{[(2S)-2-methylpyrrolidin-1-yl]methyl}phenoxy)piperidin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile; and {trans-3-[4-(3-fluoro-5-{[(2S)-2-methylpyrrolidin-1-yl]methyl}phenoxy)piperidin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

These compounds were prepared according to the method of Example 40, Step 9 using {cis-3-[4-(3-fluoro-5-{[(2*S*)-2-methylpyrrolidin-1-yl]methyl}phenoxy)piperidin-1-yl]-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile and {trans-3-[4-(3-fluoro-5-{[(2*S*)-2-methylpyrrolidin-1-yl]methyl}phenoxy)piperidin-1-yl]-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile as starting materials.

Isomer 1 (first to elute): ^{1}H NMR (500 MHz, CD_3CN): δ 10.41 (bs, 1H), 8.68 (s, 1H), 8.34 (s, 1H), 8.27 (s, 1H), 7.43 (d, 1H), 6.82 (d, 1H), 6.70 (s, 1H), 6.65 (m, 1H), 6.54 (m, 1H), 4.35 (m, 1H), 3.92 (d, 1H), 3.20 (s, 2H), 3.09 (d, 1H), 2.90-2.82 (m, 2H), 2.74-2.62 (m, 5H), 2.40 (m, 1H), 2.21 (m, 3H), 2.07 (m, 1H), 1.92 (m, 3H), 1.66 (m, 4H), 1.38 (m, 1H), 1.09 (d, 3H); LCMS $(M+H)^+$: 569.3.

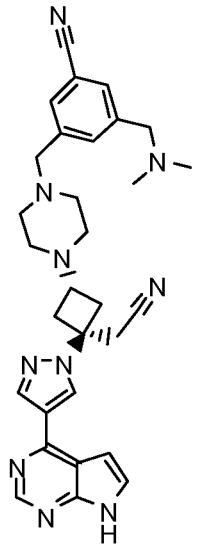
Isomer 2 (second to elute): ^{1}H NMR (500 MHz, CD_3CN): δ 10.18 (bs, 1H), 8.74 (s, 1H), 8.56 (s, 1H), 8.37 (s, 1H), 7.43 (d, 1H), 6.90 (d, 1H), 6.73 (s, 1H), 6.64 (m, 1H), 6.56 (m, 1H), 4.36 (m, 1H), 3.94 (d, 1H), 3.22 (s, 2H), 3.08 (d, 1H), 2.96 (m, 2H), 2.82 (m, 2H), 2.64 (m, 2H), 2.40 (m, 3H), 2.35-2.08 (m, 4H), 2.04 (m, 1H), 1.91 (m, 1H), 1.64 (m, 4H), 1.38 (m, 1H), 1.07 (d, 3H); LCMS $(M+H)^+$: 569.3.

Example 42. 3-[(4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)carbonyl]-5-[(dimethylamino)methyl]benzonitrile



The title compound was prepared according to the method of Example 136, using {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (40.0 mg, 0.0812 mmol, from Step 9 of Example 1a) to afford product as the free base (12.3 mg, 28%). ^{1}H NMR (400 MHz, dmso) δ 12.12 (br s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.39 (s, 1H), 7.80 (dd, 1H), 7.77 (dd, 1H), 7.62 (dd, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.06 (d, J = 3.6 Hz, 1H), 3.63 (br m, 2H), 3.47 (s, 4H), 3.29 (br m, 2H), 2.96 (tt, J = 7.5, 7.6 Hz, 1H), 2.68 – 2.52 (m, 4H), 2.40 (br m, 2H), 2.30 (br m, J = 5.6 Hz, 2H), 2.15 (s, 6H); LCMS $(M+H)^+$: 549.2.

Example 43. 3-[(4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)methyl]-5-[(dimethylamino)methyl]benzonitrile



Step A. Methyl 3-bromo-5-[(dimethylamino)methyl]benzoate

To a solution of methyl 3-bromo-5-formylbenzoate (1.8 g, 7.4 mmol, prepared as described in WO2003/048111 starting from dimethyl 5-bromoisophthalate (Alfa Aesar) in methylene chloride (20 mL) was added a solution of 2.0 M dimethylamine in tetrahydrofuran (7.4 mL, 15 mmol) and the reaction was stirred for 15 min. Sodium triacetoxyborohydride (4.7 g, 22 mmol) was then added and the resulting mixture was stirred overnight. Saturated sodium bicarbonate solution was added and the resulting mixture was extracted with ethyl acetate. The organic extract was washed twice with water, once with brine, dried over sodium sulfate, filtered and concentrated to afford product as a light yellow oil (1.87 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.03 (m, 1H), 7.90 – 7.87 (m, 1H), 7.70 – 7.67 (m, 1H), 3.91 (s, 3H), 3.42 (s, 2H), 2.24 (s, 6H); LCMS $(M+H)^+$: 272.0, 274.0.

Step B. {3-Bromo-5-[(dimethylamino)methyl]phenyl}methanol

1.0 M Diisobutylaluminum hydride in hexanes (6.2 mL, 6.2 mmol) was added dropwise to a solution of methyl 3-bromo-5-[(dimethylamino)methyl]benzoate (0.50 g, 1.8 mmol, from Step A) in tetrahydrofuran (10 mL) at -78°C. After stirring for 2 hours, the mixture was quenched with saturated potassium sodium tartrate solution and was allowed to warm to room temperature. Ethyl acetate was added and the mixture was then stirred until a biphasic solution formed. The ethyl acetate layer was washed with water

(3x), followed by brine, was dried over sodium sulfate and concentrated to give a light yellow oil (0.41 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (dd, J = 1.7 Hz, 1H), 7.37 (dd, J = 1.8 Hz, 1H), 7.24 (dd, J = 1.4, 0.7 Hz, 1H), 4.65 (s, 2H), 3.37 (s, 2H), 2.22 (s, 6H). LCMS $(M+H)^+$: 244.0, 246.0.

Step C. 3-Bromo-5-[(dimethylamino)methyl]benzaldehyde

Manganese(IV) oxide (0.71 g, 8.2 mmol) was added to a solution of {3-bromo-5-[(dimethylamino)methyl]phenyl}methanol (0.40 g, 1.6 mmol, from Step B) in toluene (10 mL). The mixture was heated to 105 °C for 2 hours, then was cooled to room temperature and was filtered and concentrated to afford a light yellow oil (0.31 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.90 (dd, J = 1.7 Hz, 1H), 7.82 – 7.69 (m, 2H), 3.46 (s, 2H), 2.25 (s, 6H).

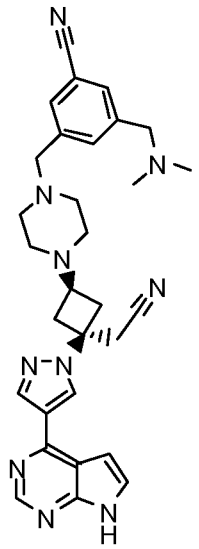
LCMS $(M+H)^+$: 241.9, 243.9.

Step D. 3-[(4-{trans-3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)methyl]-5-[(dimethylamino)methyl]benzonitrile

A solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (40. mg, 0.081 mmol, from Step 1 of Example 1b) and 3-bromo-5-[(dimethylamino)methyl]benzaldehyde (39.3 mg, 0.162 mmol, from Step C) in methylene chloride (1 mL) was treated with sodium triacetoxyborohydride (86.0 mg, 0.406 mmol) and was stirred for two hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water, 0.1 N NaOH and sat. NaCl, dried over sodium sulfate and concentrated. The residue was dissolved in N,N-dimethylformamide (1.0 mL) and zinc cyanide (57 mg, 0.48 mmol) was added. The reaction mixture was degassed by bubbling a stream of nitrogen through the mixture for 10 minutes. Tetrakis(triphenylphosphine)palladium(0) (19 mg, 0.016 mmol) was added. The reaction was heated in the microwave to 120 °C for 30 minutes. The reaction was worked up by partition between water and ethyl acetate. The ethyl acetate layer was washed twice with water, once with brine, dried over sodium sulfate and concentrated.

The residue was then stirred with 1:1 TFA:DCM for 1 hour, evaporated and stirred with 0.2 mL ethylenediamine in methanol for 30 minutes. Purification via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) followed by lyophilization afforded product as the free base (12 mg, 28%). ^{1}H NMR (400 MHz, dmso) δ 12.11 (br s, 1H), 8.81 (s, 1H), 8.69 (s, 1H), 8.41 (s, 1H), 7.63 – 7.58 (m, 3H), 7.57 (s, 1H), 7.07 (d, J = 3.6 Hz, 1H), 3.52 (s, 2H), 3.42 (s, 2H), 3.41 (s, 2H), 3.04 – 2.95 (m, 2H), 2.77 (tt, J = 7.1, 7.2 Hz, 1H), 2.47 – 2.17 (m, 10H), 2.13 (s, 6H); LCMS $(M+H)^+$: 535.3.

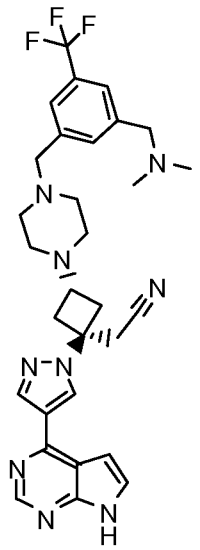
Example 44. 3-[(4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)methyl]-5-[(dimethylamino)methyl]benzonitrile



The title compound was prepared by the procedure of Example 43, Step D, using {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (40. mg, 0.081 mmol, from Step 9 of Example 1a) and 3-bromo-5-[(dimethylamino)methyl]benzaldehyde (39.3 mg, 0.162 mmol, Example 43, Step C) to afford product as the free base (14.5 mg, 33%). ^{1}H NMR (400 MHz, dmso) δ 12.11 (br s, 1H), 8.68 (s, 2H), 8.38 (s, 1H), 7.62 – 7.58 (m, 3H), 7.56 (s, 1H), 7.06 (d, J = 3.6 Hz, 1H), 3.50 (s, 2H), 3.46 (s, 3H), 3.42 (s, 2H), 2.90

(tt, J = 7.5, 7.6 Hz, 1H), 2.67 – 2.53 (m, 4H), 2.47 – 2.16 (m, 8H), 2.13 (s, 6H); LCMS $(M+H)^+$: 535.2.

Example 45. {trans-3-{4-[3-[(dimethylamino)methyl]-5-(trifluoromethyl)benzyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step A. 1-[3-Bromo-5-(trifluoromethyl)phenyl]-N,N-dimethylmethanamine

To a solution of 3-bromo-5-(trifluoromethyl)benzaldehyde (2.0 g, 7.9 mmol, Combi-blocks) in methylene chloride (10 mL) was added a solution of 2.0 M dimethylamine in tetrahydrofuran (7.9 mL, 16 mmol) and the reaction was stirred for 15 minutes at room temperature. The reaction was then cooled to 0°C and sodium triacetoxyborohydride (2.5 g, 12 mmol) was added. The resulting mixture was warmed to room temperature and was stirred for 24 hours. The solvents were removed *in vacuo*. Saturated sodium bicarbonate solution was added and the resulting mixture was extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. Purification by silica gel column chromatography, eluting with a gradient from 10-40% ethyl acetate in hexanes afforded product as a colorless oil (1.58 g, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.65 (s, 1H), 7.57 – 7.46 (m, 1H), 3.45 (s, 2H), 2.25 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.10 (s); LCMS $(M+H)^+$: 282.0, 284.0.

Step B. 3-[(Dimethylamino)methyl]-5-(trifluoromethyl)benzaldehyde

2.5 M n-Butyllithium in hexanes (0.47 mL, 1.2 mmol) was added dropwise to a solution of 1-[3-bromo-5-(trifluoromethyl)phenyl]-N,N-dimethylmethanamine (0.30 g, 1.1 mmol, from Step A) in THF (6.0 mL) at -78 °C. After stirring at this temperature for 20 minutes, N,N-dimethylformamide (160 μL, 2.1 mmol) was added dropwise. After a total reaction time of 50 minutes at -78°C, the reaction was quenched with 1.0 M Hydrogen chloride in water (2.1 mL, 2.1 mmol). After warming to room temperature, the mixture was diluted with more water, treated with saturated sodium bicarbonate to achieve pH 7, then extracted with ethyl acetate (EtOAc). The combined extracts were washed with water (3x), brine, dried over sodium sulfate and concentrated to give a light yellow oil, a 4:1 mixture of the desired together with de-bromination byproduct, which was used without further purification (0.2 g, 60%).

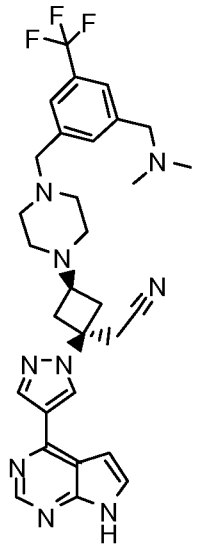
^{1}H NMR (300 MHz, $CDCl_3$) δ 10.06 (d, J = 0.9 Hz, 1H), 8.03 (s, 2H), 7.87 (s, 1H), 3.55 (s, 2H), 2.27 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.15 (s); LCMS $(M+H)^+$: 232.1.

Step C. {trans-3-{4-[3-[(Dimethylamino)methyl]-5-(trifluoromethyl)benzyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

A solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, from Step 1 of Example 1b) and 3-[(dimethylamino)methyl]-5-(trifluoromethyl)benzaldehyde (0.0352 g, 0.122 mmol, from Step B) in methylene chloride (DCM) (1 mL) was treated with sodium triacetoxyborohydride (0.0645 g, 0.304 mmol) and stirred overnight. The mixture was quenched with 0.1 N NaOH and extracted with DCM. The combined organic extracts were washed with three portions of water, followed by brine, dried over sodium sulfate and concentrated. The residue was stirred with 1:1 TFA:DCM for 1 hour, evaporated and then stirred with 0.2 mL ethylenediamine in methanol for 30 minutes. Purification via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH), followed by lyophilization afforded product as the free base (21.4 mg, 61%).

^{1}H NMR (400 MHz, dmso) δ 12.13 (br s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.41 (s, 1H), 7.60 (d, *J* = 3.6 Hz, 1H), 7.55 – 7.47 (m, 3H), 7.08 (d, *J* = 3.6 Hz, 1H), 3.56 (s, 2H), 3.46 (s, 2H), 3.41 (s, 2H), 3.04 – 2.93 (m, 2H), 2.77 (tt, *J* = 7.2, 7.2 Hz, 1H), 2.48 – 2.18 (m, 10H), 2.14 (s, 6H); ^{19}F NMR (376 MHz, dmso) δ -61.25 (s); LCMS (M+H)$^+$: 578.3.

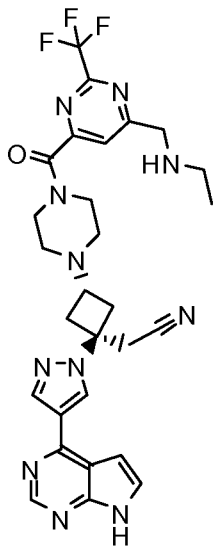
Example 46. {cis-3-{4-[3-[(dimethylamino)methyl]-5-(trifluoromethyl)benzyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



The title compound was prepared by the method of Example 45, using {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, from Step 9 of Example 1a) and 3-[(dimethylamino)methyl]-5-(trifluoromethyl)benzaldehyde (0.0352 g, 0.122 mmol, from Example 45, Step B) to afford product as the free base (29.4 mg, 84%). ^{1}H NMR (400 MHz, dmso) δ 12.14 (br s, 1H), 8.69 (s, 1H), 8.68 (s, 1H), 8.39 (s, 1H), 7.60 (d, *J* = 3.5 Hz, 1H), 7.54 – 7.46 (m, 3H), 7.06 (d, *J* = 3.6 Hz, 1H), 3.54 (s, 2H), 3.46 (s, 4H), 2.89 (tt, *J* = 7.8, 8.0 Hz, 1H), 2.64 – 2.16 (m, 12H), 2.13 (s, 6H). ^{19}F NMR (376 MHz, dmso) δ -61.25 (s); LCMS (M+H)$^+$: 578.2.

Example 47. {trans-3-(4-{[6-[(ethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-

yl]cyclobutyl}acetonitrile



Step A. Ethyl 6-(bromomethyl)-2-(trifluoromethyl)pyrimidine-4-carboxylate

A solution of ethyl 6-methyl-2-(trifluoromethyl)pyrimidine-4-carboxylate (2.00 g, 8.54 mmol, prepared as described in WO2007/090748) in acetic acid (12 mL) was treated with bromine (1.36 g, 8.54 mmol) and the reaction was heated to 80 °C in a sealed vial for 30 minutes, at which time, the color of bromine was dissipated. The acetic acid was removed *in vacuo* and was followed by dissolving of the residue in toluene and removal of solvent *in vacuo*. The percent by weight of desired component in the mixture (containing unreacted starting material and overbrominated product) was determined by NMR and the mixture used without further purification (1.62 g, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (s, 1H), 4.60 (s, 2H), 4.54 (q, 2H), 1.46 (t, 3H); LCMS $(M+H)^+$: 313.0, 315.0

Step B. Ethyl 6-[(acetyloxy)methyl]-2-(trifluoromethyl)pyrimidine-4-carboxylate

Ethyl 6-(bromomethyl)-2-(trifluoromethyl)pyrimidine-4-carboxylate (1.62 g, 5.17 mmol, from Step A) was dissolved in acetonitrile (15 mL) and sodium acetate (2.8 g, 34 mmol) was added. The mixture was heated to 80 °C for 4 hours, then allowed to stand at room temperature overnight. Acetonitrile was removed *in vacuo*. The residue was partitioned between water and ethyl acetate and the aqueous layer was extracted with two further portions of ethyl acetate. The combined extracts were washed with water, then

brine, dried over sodium sulfate, filtered and concentrated. Flash chromatography, eluting with a gradient from 0-60% EtOAc/hexanes afforded purified product (0.95 g, 63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (s, 1H), 5.36 (s, 2H), 4.53 (q, 2H), 2.25 (s, 3H), 1.46 (t, 3H); LCMS $(M+H)^+$: 293.0.

Step C. 6-[(Acetyloxy)methyl]-2-(trifluoromethyl)pyrimidine-4-carboxylic acid

A solution of ethyl 6-[(acetyloxy)methyl]-2-(trifluoromethyl)pyrimidine-4-carboxylate (0.95 g, 3.2 mmol, from Step B) in tetrahydrofuran (8.7 mL) at 0 °C was treated with lithium hydroxide, monohydrate (140 mg, 3.2 mmol) in water (1.3 mL). The reaction was stirred for 15 minutes, then was treated with 1N HCl to pH~4 while still in the ice bath. THF was removed from the mixture *in vacuo*. The product was extracted first with ethyl acetate, then with several portions of 10% iPrOH in $CHCl_3$, including periodic adjustment of pH as necessary. The extracts were combined and dried over sodium sulfate, filtered and concentrated to afford a yellow oil, which was used without further purification (0.86 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (s, 1H), 5.35 (s, 2H), 2.23 (s, 3H); LCMS $(M+H)^+$: 265.0.

Step D. {trans-3-(4-{[6-(Hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

Triethylamine (3.5 mL, 25 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (3.11 g, 7.02 mmol) were added to a solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (3.01 g, 6.11 mmol, from Step 1 of Example 1b) and 6-[(acetyloxy)methyl]-2-(trifluoromethyl)pyrimidine-4-carboxylic acid (1.91 g, 7.23 mmol, from Step C) in N,N-Dimethylformamide (50. mL). After stirring for 1 hour, the reaction mixture was partitioned between ethyl acetate and water. The aqueous portion was extracted with two further portions of ethyl acetate. The combined organic extracts were washed with water, brine, dried over sodium sulfate, filtered and concentrated. The

product was purified by flash chromatography, eluting with a gradient from 0-5% MeOH/ethyl acetate to give 4.5 g brown oil. The oil was dissolved in tetrahydrofuran (50.0 mL), and a solution of lithium hydroxide, monohydrate (0.31 g, 7.3 mmol) in water (12 mL, 670 mmol) was added. After stirring for 30 minutes, 1 N HCl was used to adjust the pH to 7. The mixture was diluted with water, and extracted with EtOAc. The combined organic extracts were washed twice with water, once with brine, dried over sodium sulfate and concentrated to afford the product as a light yellow solid (3.24 g, 76%).

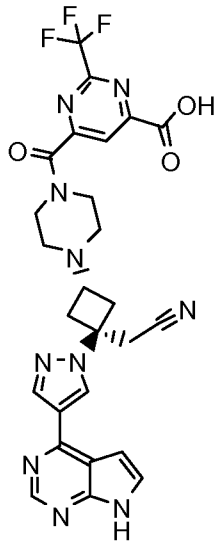
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.46 (s, 1H), 8.32 (s, 1H), 7.97 (s, 1H), 7.41 (d, J = 3.7 Hz, 1H), 6.81 (d, J = 3.7 Hz, 1H), 5.67 (s, 2H), 4.91 (s, 2H), 3.92 – 3.78 (m, 2H), 3.71 – 3.57 (m, 2H), 3.59 – 3.43 (m, 2H), 3.34 (br s, 1H), 3.20 (s, 2H), 3.12 – 2.83 (m, 3H), 2.55 – 2.36 (m, 6H), 0.99 – 0.84 (m, 2H), -0.06 (s, 9H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -70.74 (s); LCMS $(M+H)^+$: 697.3.

Step E. {trans-3-(4-{[6-[(Ethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

A solution of methanesulfonyl chloride (22 μL, 0.28 mmol) in methylene chloride (1.5 mL) was added to a mixture of {trans-3-(4-{[6-(hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.15 g, 0.22 mmol, from Step D) and triethylamine (0.060 mL, 0.43 mmol) in methylene chloride (7.1 mL). After stirring for 15 minutes, ethylamine (0.5 mL, 9 mmol) was added. After 1 hour, solvents were removed *in vacuo* and the residue was dissolved in a 1:1 mixture of TFA/DCM, stirred for one hour, then concentrated again. The residue was redissolved in 10 ml MeOH, and 0.5 ml ethylenediamine was added. After deprotection was complete, the product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) and lyophilized to afford product as the free base (37 mg, 28%).

^{1}H NMR (400 MHz, dmso) δ 12.13 (s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.96 (s, 1H), 7.60 (dd, *J* = 3.6, 2.3 Hz, 1H), 7.07 (dd, *J* = 3.6, 1.7 Hz, 1H), 3.95 (s, 2H), 3.77 – 3.63 (m, 2H), 3.43 (s, 2H), 3.41 – 3.35 (m, 2H), 3.06 – 2.95 (m, 2H), 2.85 (tt, *J* = 7.3, 7.3 Hz, 1H), 2.58 (q, *J* = 7.1 Hz, 2H), 2.47 – 2.40 (m, 2H), 2.40 – 2.33 (m, 2H), 2.33 – 2.25 (m, 2H), 1.04 (t, *J* = 7.1 Hz, 3H); ^{19}F NMR (376 MHz, dmso) δ -69.43 (s); LCMS $(M+H)^+$: 594.3

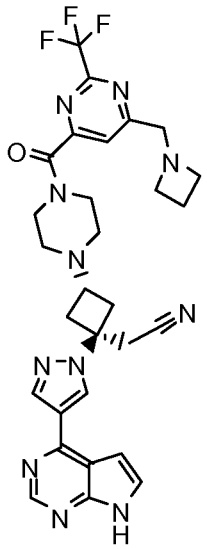
Example 48. 6-[(4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)carbonyl]-2-(trifluoromethyl)pyrimidine-4-carboxylic acid



6-[(4-{trans-3-(Cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)carbonyl]-2-(trifluoromethyl)pyrimidine-4-carboxylic acid was produced as a byproduct of the hydrolysis reaction described in Example 47, Step D. This product could be purified from that reaction mixture via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH). The product was deprotected by stirring with 1:1TFA:DCM for 1 hour, followed by evaporation and stirring with excess ethylenediamine in methanol. After deprotection was complete, the product was again purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) and lyophilized to afford product. ^{1}H NMR (400 MHz,

CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.39 (s, 1H), 8.21 (s, 1H), 7.50 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 3.7 Hz, 1H), 3.91 – 3.77 (m, 2H), 3.61 – 3.46 (m, 2H), 3.35 (s, 2H), 3.14 – 3.02 (m, 2H), 3.03 – 2.88 (m, 1H), 2.63 – 2.36 (m, 6H); LCMS $(M+H)^+$: 581.2

Example 49. {trans-3-(4-{[6-(azetidin-1-ylmethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step A. Ethyl 6-(azetidin-1-ylmethyl)-2-(trifluoromethyl)pyrimidine-4-carboxylate

Azetidine (0.62 mL, 9.2 mmol, Aldrich) was added to a solution of ethyl 6-(bromomethyl)-2-(trifluoromethyl)pyrimidine-4-carboxylate (1.76 g, 4.16 mmol, prepared in the manner outlined in Example 47, Step A) in methylene chloride (39 mL). and the reaction was stirred for 20 minutes. Solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel, eluting with a gradient from 0-5% MeOH in DCM to afford product (0.74 g, 61%); LCMS $(M+H)^+$: 290.0.

Step B . 6-(Azetidin-1-ylmethyl)-2-(trifluoromethyl)pyrimidine-4-carboxylic acid dihydrochloride

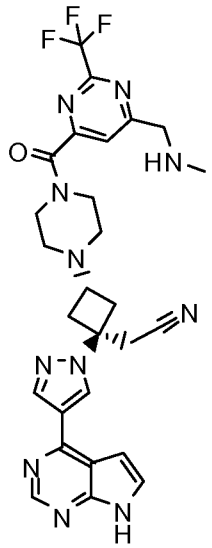
Lithium hydroxide, monohydrate (108 mg, 2.57 mmol) was added to a mixture of ethyl 6-(azetidin-1-ylmethyl)-2-(trifluoromethyl)pyrimidine-4-carboxylate (0.34 g, 1.2 mmol, from Step A) in tetrahydrofuran (6.0 mL) and water (1.5 mL). After 15 minutes,

the THF was removed *in vacuo* and the mixture was treated with 1.0 M hydrogen chloride in water (5.3 mL, 5.3 mmol), and acetonitrile (7.0 mL) . The mixture was then filtered and concentrated to afford the product as a yellow solid. LCMS $(M+H)^+$: 262.1.

Step C. {trans-3-(4-{[6-(Azetidin-1-ylmethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

{trans-3-Piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (20.0 mg, 0.0406 mmol, from Step 1 of Example 1b) was added to a mixture of 6-(azetidin-1-ylmethyl)-2-(trifluoromethyl)pyrimidine-4-carboxylic acid dihydrochloride (27 mg, 0.061 mmol, from Step B), triethylamine (33.9 μL, 0.244 mmol) and N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium Hexafluorophosphate (21.6 mg, 0.0568 mmol) in DCM (0.4 mL) and THF (0.45 mL) that was pre-stirred for 15 minutes. After stirring overnight, the mixture was diluted with EtOAc, washed successively with water, 0.1 N NaOH, and brine, dried over sodium sulfate, decanted and concentrated. The crude product was deprotected by stirring with 1:1 DCM/TFA for one hour, removal of solvents *in vacuo*, and stirring with ethylenediamine (0.1 mL) in MeOH (1 mL). Purification via preparative HPLC-MS (C18 eluting with a gradient of $MeCN/H_2O$ containing 0.15% NH_4OH) followed by lyophilization afforded the product as the free base (6.2 mg, 25%). ^1H NMR (400 MHz, dmso) δ 12.13 (s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.82 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 3.82 (s, 2H), 3.75 – 3.64 (m, 2H), 3.43 (s, 2H), 3.39 – 3.35 (m, 2H), 3.28 (t, J = 7.0 Hz, 4H), 3.06 – 2.96 (m, 2H), 2.85 (tt, J = 7.0, 7.4 Hz, 1H), 2.47 – 2.40 (m, 2H), 2.40 – 2.33 (m, 2H), 2.33 – 2.26 (m, 2H), 2.04 (p, J = 7.1 Hz, 2H); ^{19}F NMR (376 MHz, dmso) δ -69.49 (s); LCMS $(M+H)^+$: 606.2.

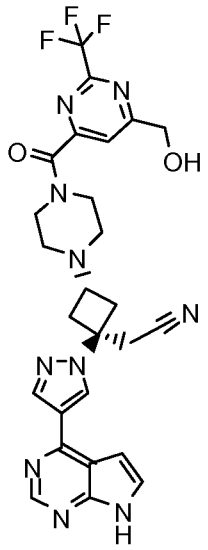
Example 50. {trans-3-(4-{[6-[(methylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Methanesulfonyl chloride (0.006 mL, 0.08 mmol) was added to a solution of {trans-3-(4-{[6-(hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.043 mmol, from Example 47, Step D) and N,N-diisopropylethylamine (0.025 g, 0.19 mmol) in methylene chloride (1 mL). When mesylate formation was complete as determined by LCMS, 10.6 M methylamine in ethanol (0.20 mL, 2.2 mmol) was added (33 wt% in ethanol, Aldrich). After stirring for a total of 2 hours, solvent and excess reagents were removed *in vacuo*. To deprotect, trifluoroacetic Acid (1 mL) was added. After stirring for 2 hours, the solvents were evaporated and the residue was dissolved in methanol (1 mL) and ethylenediamine (0.2 mL, 3 mmol) was added. After 30 minutes, the deprotection was complete and the product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) and lyophilized to afford the product as the free base (5 mg, 20%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.88 (s, 1H), 7.51 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 4.00 (s, 2H), 3.89 – 3.79 (m, 2H), 3.58 – 3.50 (m, 2H), 3.34 (s, 2H), 3.13 – 3.02 (m, 2H), 2.97 (tt, J = 7.0, 7.1 Hz, 1H), 2.58 – 2.43 (m, 6H); ^{19}F NMR (376 MHz, CD_3OD) δ -72.35 (s); LCMS $(M+H)^+$: 580.2.

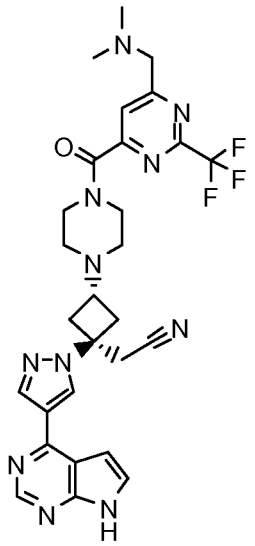
Example 51. {trans-3-(4-{[6-(hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-

yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



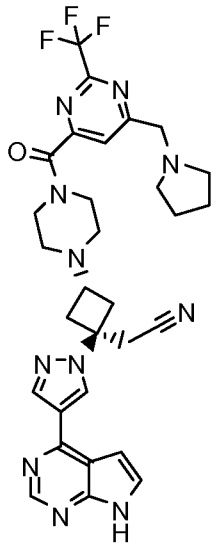
{trans-3-(4-{[6-(Hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (prepared as in Example 47, Step D) was stirred with 1:1 TFA/DCM for 1 hour. Solvents were removed *in vacuo* and the residue was then stirred with excess ethylenediamine in methanol overnight. Purification via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) followed by lyophilization afforded the product as the free base. ^1H NMR (500 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.84 (s, 1H), 8.50 (s, 1H), 8.33 (s, 1H), 7.96 (s, 1H), 7.38 (dd, J = 3.7, 2.1 Hz, 1H), 6.82 (dd, J = 3.7, 1.8 Hz, 1H), 4.93 (d, J = 4.6 Hz, 2H), 3.87 (br m, 2H), 3.68 (br m, 2H), 3.22 (s, 2H), 3.14 – 2.88 (m, 3H), 2.80 (t, J = 5.6 Hz, 1H), 2.66 – 2.27 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -70.77 (s); LCMS $(M+H)^+$: 551.2

Example 52. {trans-3-(4-{[6-[(dimethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Triethylamine (0.16 mL, 1.1 mmol) and methanesulfonyl chloride (58 μL, 0.75 mmol) were added sequentially to a solution of {trans-3-(4-{[6-(hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.4 g, 0.6 mmol, prepared as in Example 47, Step D) in methylene chloride (19 mL, 3.0E2 mmol). After 15 minutes, 2.0 M dimethylamine in THF (2.87 mL, 5.74 mmol, Aldrich) was added. After 2 hours, the mixture was concentrated, the residue was dissolved in a 1:1 mixture of TFA/DCM, stirred for one hour, then concentrated again. The residue was redissolved in 10 mL MeOH, and 1.0 mL of ethylenediamine was added. After complete deprotection, the product was purified via preparative HPLC-MS (C18 eluting with a gradient from 20-38% MeCN/H_2O containing 0.15% NH_4OH and lyophilized to afford product as the free base (134 mg, 38%). ^1H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.94 (s, 1H), 7.51 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 3.7 Hz, 1H), 3.92 – 3.77 (m, 4H), 3.64 – 3.45 (m, 2H), 3.35 (s, 2H), 3.16 – 3.02 (m, 2H), 2.97 (tt, J = 7.1, 7.3 Hz, 1H), 2.62 – 2.41 (m, 6H), 2.40 (s, 6H); ^{19}F NMR (376 MHz, CD_3OD) δ -72.31 (s); LCMS $(M+H)^+$: 594.2

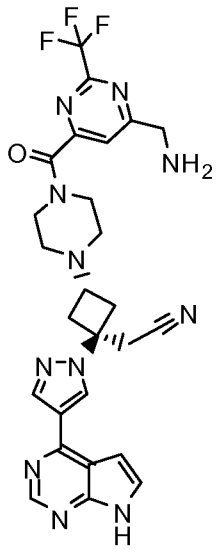
Example 53. {trans-3-(4-{[6-(pyrrolidin-1-ylmethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Methanesulfonyl chloride (0.022 mL, 0.29 mmol) was added to a solution of {trans-3-(4-{[6-(hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.100 g, 0.144 mmol, prepared as in Example 47, Step D) and N,N-diisopropylethylamine (0.083 g, 0.64 mmol) in DCM (3 mL). When mesylate formation was complete as determined by LCMS, pyrrolidine (0.120 mL, 1.44 mmol, Aldrich) was added. The reaction was stirred for 40 hours. The reaction was partitioned between water and ethyl acetate and the aqueous portion was extracted a further two times with ethyl acetate. The combined extracts were dried over sodium sulfate, decanted and concentrated. The crude product was stirred with 1:1 TFA:DCM for 2 hours. The solvents were evaporated and replaced with methanol (3 mL) and ethylenediamine (0.7 mL, 10 mmol) and the deprotection stirred for 30 minutes. Purification via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH). followed by purification via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.1% TFA). followed by purification again via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) afforded product, after lyophilization, as the free base. ^1H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.93 (s, 1H), 7.51 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 3.94 (s, 2H), 3.89 – 3.77 (m, 2H), 3.59 – 3.46 (m, 2H), 3.34 (s, 2H), 3.13 – 3.03 (m, 2H), 2.97 (tt, J = 7.0, 7.2 Hz, 1H), 2.72 – 2.61 (m, 4H), 2.62 –

2.40 (m, 6H), 1.91 – 1.71 (m, 4H); ^{19}F NMR (376 MHz, CD_3OD) δ -72.31 (s); LCMS $(M+H)^+$: 620.3

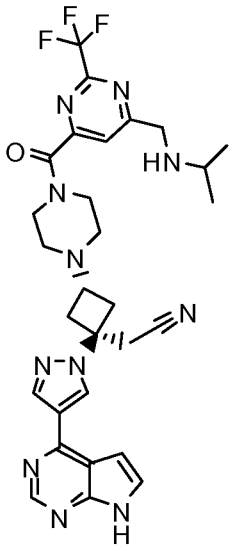
Example 54. {trans-3-(4-{[6-(aminomethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Triethylamine (0.012 mL, 0.089 mmol) and methanesulfonyl chloride (4.5 μL, 0.058 mmol) were added to a solution of {trans-3-(4-{[6-(hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (31 mg, 0.044 mmol, prepared as in Example 47, Step D) in methylene chloride (1.5 mL). After 15 minutes, the mixture was concentrated *in vacuo* and 7.0 M ammonia in methanol (0.6 mL, 4 mmol) was added. After 2 hours, solvents and excess reagents were removed *in vacuo* and the residue was dissolved in a 1:1 mixture of TFA/DCM and stirred for one hour, then concentrated again. Deprotection was completed by stirring the resulting residue in 1 mL MeOH containing 0.2 mL of ethylenediamine. Purification via preparative HPLC-MS (C18 eluting with a gradient of $MeCN/H_2O$ containing 0.15% NH_4OH) followed by lyophilization afforded product as the free base (2.6 mg, 10%).

^{1}H NMR (400 MHz, dmso) δ 12.13 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 8.03 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 3.94 (s, 2H), 3.79 – 3.65 (m, 2H), 3.43 (s, 2H), 3.40 – 3.36 (m, 2H), 3.09 – 2.96 (m, 2H), 2.84 (tt, J = 7.3, 7.4 Hz, 1H), 2.47 – 2.24 (m, 6H); ^{19}F NMR (376 MHz, dmso) δ -69.42 (s); LCMS $(M+H)^+$: 566.3.

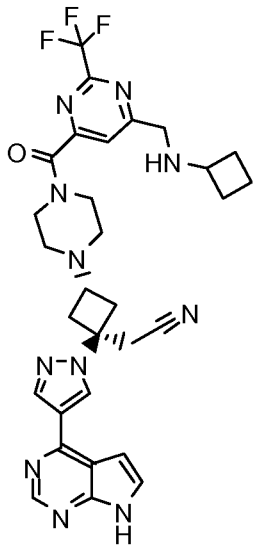
Example 55. {trans-3-(4-{[6-[(isopropylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Triethylamine (0.012 mL, 0.089 mmol) and methanesulfonyl chloride (4.5 μL, 0.058 mmol) were added to a solution of {trans-3-(4-{[6-(hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (31 mg, 0.044 mmol, prepared as in Example 47, Step D) in methylene chloride (1.5 mL). After 15 minutes, 2-propanamine (37.9 μL, 0.445 mmol, Aldrich) was added. After stirring overnight, solvent and excess reagents were removed *in vacuo*. The residue was dissolved in a 1:1 mixture of TFA/DCM, stirred for one hour, then concentrated again. The residue was redissolved in 1 mL MeOH and 0.2 mL of

ethylenediamine was added. Purification via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) followed by lyophilization afforded product as the free base (4.3 mg, 16%). ^{1}H NMR (400 MHz, dmso) δ 12.14 (s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.99 (s, 1H), 7.61 (d, J = 3.6 Hz, 1H), 7.08 (d, J = 3.6 Hz, 1H), 3.94 (s, 2H), 3.78 – 3.63 (m, 2H), 3.43 (s, 2H), 3.41 – 3.37 (m, 2H), 3.07 – 2.96 (m, 2H), 2.84 (tt, J = 7.2, 7.2 Hz, 1H), 2.74 (hept, J = 6.7, 6.3 Hz, 1H), 2.48 – 2.40 (m, 2H), 2.40 – 2.32 (m, 2H), 2.32 – 2.21 (m, 2H), 1.00 (d, J = 6.2 Hz, 6H); LCMS $(M+H)^+$: 608.3.

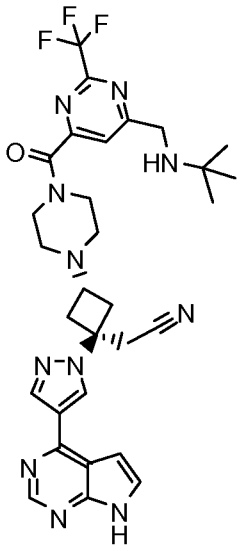
Example 56. {trans-3-(4-{[6-[(cyclobutylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



The title compound was prepared by a modification of Example 55, starting from {trans-3-(4-{[6-(hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (31 mg, 0.044 mmol, prepared as in Example 47, Step D) and using cyclobutanamine (40 μL, 0.4 mmol, Aldrich), but with stirring at 40 °C overnight after addition of the amine, to afford product as the free base (9.0 mg, 33%). ^{1}H NMR (300 MHz, dmso) δ 12.12 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.95 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 3.86 (s, 2H), 3.76 – 3.60

(m, 2H), 3.26 – 3.10 (m, 1H), 3.43 (s, 2H), 3.40 – 3.35 (m, 2H), 3.10 – 2.93 (m, 2H), 2.84 (tt, J = 6.7, 6.5 Hz, 1H), 2.75 (br s, 1H), 2.46 – 2.20 (m, 6H), 2.14 – 1.94 (m, 2H), 1.80 – 1.38 (m, 4H); ^{19}F NMR (282 MHz, dmso) δ -69.43 (s); LCMS $(M+H)^+$: 620.2.

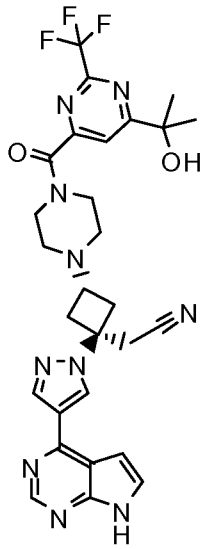
Example 57. {trans-3-(4-{[6-[(tert-butylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



The title compound was prepared as in Example 56, starting with {trans-3-(4-{[6-(hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (81 mg, 0.12 mmol, prepared as in Example 47, Step D) and using tert-Butylamine (100 μL, 1 mmol, Aldrich) to afford product as the free base (19.5 mg, 26%). ^{1}H NMR (400 MHz, dmso) δ 12.13 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 8.02 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 3.92 (s, 2H), 3.73 – 3.60 (m, 2H), 3.43 (s, 2H), 3.40 – 3.35 (m, 2H), 3.07 – 2.94 (m, 2H), 2.84 (tt, J = 7.1, 7.2 Hz, 1H), 2.46 – 2.40 (m, 2H), 2.40 – 2.33 (m, 3H), 2.33 – 2.25 (m, 2H), 1.07 (s, 9H); ^{19}F NMR (376 MHz, dmso) δ -69.41 (s); LCMS $(M+H)^+$: 622.2.

Example 58. {trans-3-(4-{[6-(1-hydroxy-1-methylethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-

d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step A. Ethyl 6-isopropyl-2-(trifluoromethyl)pyrimidine-4-carboxylate

To a solution of 2,2,2-trifluoroethanimidamide (7.08 g, 53.7 mmol, Matrix) in ethanol (85 mL, 1400 mmol) was added ethyl (3Z)-4-hydroxy-5-methyl-2-oxohex-3-enoate (10.00 g, 53.70 mmol, Alfa Aesar). The mixture was then cooled in an ice bath, and a solution of hydrogen chloride in ethanol (84 mL, prepared by bubbling HCl gas through the ethanol for 10 minutes) was added. The reaction was allowed to warm to room temperature and stir overnight. The mixture was added dropwise to a saturated solution of sodium bicarbonate. After complete neutralization was achieved, ethanol was removed *in vacuo*. The product was extracted with three portions of DCM. The combined extracts were dried over sodium sulfate, filtered and evaporated. The crude product was purified by flash chromatography on silica gel, eluting with a gradient from 0-25% EtOAc/Hexanes (9.14 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 4.52 (q, J = 7.1 Hz, 2H), 3.22 (hept, J = 6.9 Hz, 1H), 1.45 (t, J = 7.1 Hz, 3H), 1.38 (d, J = 6.9 Hz, 6H); LCMS $(M+H)^+$: 263.1

Step B. 6-(1-Hydroxy-1-methylethyl)-2-(trifluoromethyl)pyrimidine-4-carboxylic acid

A solution of ethyl 6-isopropyl-2-(trifluoromethyl)pyrimidine-4-carboxylate (2.00 g, 7.63 mmol, from Step A) in tetrahydrofuran (40 mL) was added to 1.0 M potassium

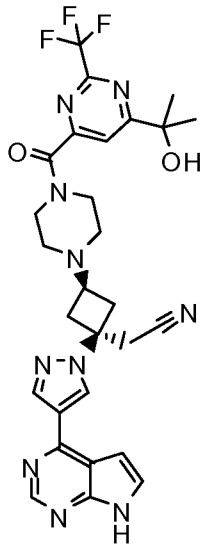
tert-butoxide in THF (22.9 mL, 22.9 mmol) held at -40 °C. After stirring for 45 minutes at this temperature, oxygen was introduced below the surface of the reaction solution via a syringe attached to a balloon containing oxygen. The oxygen was bubbled subsurface periodically (by addition and removal of an outlet) for 20 minutes, while maintaining the reaction temperature between -40 to -30 °C. The reaction was then allowed to slowly reach room temperature with periodic bubbling of oxygen through the solution. Near a temperature of -30 deg C, the reaction turned from purple to orange in color. The reaction was kept under atmospere of oxygen overnight, at which time the reaction was quenched with water and sodium sulfite (2 g, 20 mmol) was added. Lithium hydroxide, monohydrate (0.928 g, 22.1 mmol) was also added and the reaction was stirred overnight. Concentrated HCl was added dropwise into the reaction to achieve pH between 3 and 4. The layers were separated and the THF layer was reserved for addition to the subsequent two ethyl acetate extractions. The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated, then azeotroped twice with MeOH to afford a yellow syrup which was used without further purification (1.7 g, 62%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1H), 1.57 (s, 6H); LCMS $(M+H)^+$: 251.0

Step C. {trans-3-(4-{[6-(1-Hydroxy-1-methylethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

{trans-3-Piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (1.145 g, 2.324 mmol, from Step 1 of Example 1b), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (1214 mg, 2.746 mmol) and triethylamine (1.6 mL, 11 mmol) were added to a solution of 6-(1-hydroxy-1-methylethyl)-2-(trifluoromethyl)pyrimidine-4-carboxylic acid (0.572 g, 2.29 mmol, from Step B) in N,N-dimethylformamide (60 mL, 700 mmol). After stirring overnight, the reaction mixture was partitioned between ethyl acetate and brine, and the aqueous was extracted three times with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and concentrated. The SEM-protected product was purified by

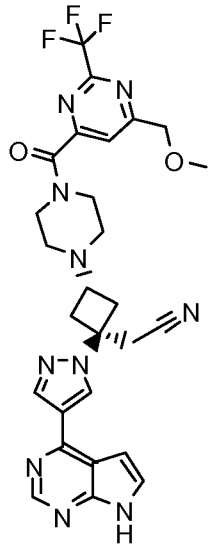
flash chromatography on silica gel, eluting with a gradient from 0-10% MeOH in DCM. The product was stirred with TFA:DCM (1:1) for 1 hour, and solvents were removed *in vacuo*. The resulting residue was stirred with excess ethylenediamine in methanol until the deprotection was complete. The solution was filtered and purified via successive preparative HPLC-MS runs at pH10 (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH), then pH2 (C18 eluting with a gradient of MeCN/H_2O containing 0.1% TFA). After lyophilization, the product was free based by dissolution in ethyl acetate and washing with saturated sodium bicarbonate, then extraction of the basic aqueous layer with two further portions of ethyl acetate. The combined extracts were washed with water, then brine, dried over sodium sulfate, filtered and concentrated. To afford an easily handled solid, the sample was re-dissolved in MeCN and H_2O, frozen and lyophilized to afford desired compound as the free base (0.18 g, 13%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.85 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 8.05 (s, 1H), 7.40 (dd, J = 3.8, 1.6 Hz, 1H), 6.81 (d, J = 3.4 Hz, 1H), 3.91 – 3.76 (m, 2H), 3.72 – 3.57 (m, 2H), 3.21 (s, 2H), 3.11 – 3.01 (m, 2H), 2.97 (tt, J = 6.4, 7.2 Hz, 1H), 2.60 – 2.37 (m, 6H), 1.62 (s, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -70.70 (s); LCMS $(M+H)^+$: 595.1

Example 59. {cis-3-(4-{[6-(1-hydroxy-1-methylethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



6-(1-Hydroxy-1-methylethyl)-2-(trifluoromethyl)pyrimidine-4-carboxylic acid (0.010 g, 0.040 mmol, Example 58, Step B) was dissolved in N,N-dimethylformamide (1 mL, 10 mmol) and to this was added {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.020 g, 0.040 mmol, from Step 9 of Example 1a), followed by benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (21.2 mg, 0.0480 mmol) and triethylamine (0.028 mL, 0.20 mmol). After stirring overnight, the reaction mixture was partitioned between ethyl acetate and water, and the aqueous portion was extracted a further two times. The combined extracts were dried over sodium sulfate, filtered and concentrated. The product was deprotected by stirring with TFA:DCM (1:1) for 1 hour, followed by evaporation and stirring with excess ethylenediamine in methanol until the deprotection was complete. The product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) to afford product as the free base (0.01 g, 40%). ^1H NMR (400 MHz, dmso) δ 12.13 (s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.40 (s, 1H), 8.06 (s, 1H), 7.60 (dd, J = 3.6, 2.3 Hz, 1H), 7.06 (dd, J = 3.6, 1.8 Hz, 1H), 5.78 (s, 1H), 3.76 – 3.62 (m, 2H), 3.47 (s, 2H), 3.41 – 3.24 (m, 2H), 2.97 (br m, 1H), 2.62 (br m, 4H), 2.44 (br m, 2H), 2.32 (br m, 2H), 1.47 (s, 6H); ^{19}F NMR (376 MHz, dmso) δ -69.40 (s); LCMS $(M+H)^+$: 595.2

Example 60. {trans-3-(4-{[6-(methoxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step A. 6-(Methoxymethyl)-2-(trifluoromethyl)pyrimidine-4-carboxylic acid

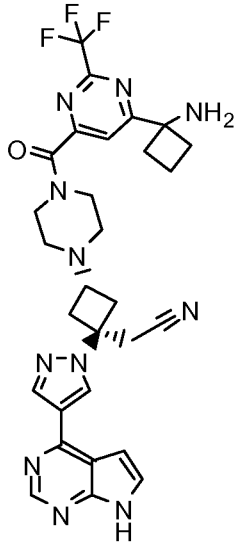
Potassium carbonate (1.2 g, 8.7 mmol) was added to a solution of ethyl 6-(bromomethyl)-2-(trifluoromethyl)pyrimidine-4-carboxylate (0.65 g, 1.2 mmol, prepared in the manner outlined in Example 47, Step A) in methanol (10 mL). After stirring for 2 hours, the reaction was then treated with 1N HCl to achieve pH 4, was diluted with water and extracted with six portions of 10% isopropanol in chloroform. The combined extracts were dried over sodium sulfate and concentrated to afford product as an oil which was used without further purification (0.25 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H), 4.74 (s, 2H), 3.58 (s, 3H); LCMS $(M+H)^+$: 237.1.

Step B. {trans-3-(4-{[6-(Methoxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

Triethylamine (36 μL, 0.26 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (34.5 mg, 0.0779 mmol) were added to a solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-

yl]cyclobutyl}acetonitrile (32 mg, 0.065 mmol, from Step 1 of Example 1b) and 6-(methoxymethyl)-2-(trifluoromethyl)pyrimidine-4-carboxylic acid (18 mg, 0.078 mmol, from Step A) in N,N-dimethylformamide (0.64 mL, 8.3 mmol). After stirring for 1 hour, the mixture was diluted with EtOAc, washed with water (3x), then brine, then dried over sodium sulfate, filtered and concentrated. The crude mixture was stirred in a 1:1 mixture of TFA:DCM for one hour, then was concentrated. The residue was dissolved in 1.0 mL MeOH, and 200 µl ethylenediamine was added. When deprotection was complete, the product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) to afford product as the free base (5.0 mg, 13%). ^{1}H NMR (300 MHz, dmso) δ 12.12 (br s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.87 (s, 1H), 7.60 (d, *J* = 3.5 Hz, 1H), 7.07 (d, *J* = 3.6 Hz, 1H), 4.68 (s, 2H), 3.77 – 3.58 (m, 2H), 3.46 – 3.36 (m, 7H), 3.11 – 2.94 (m, 2H), 2.85 (tt, *J* = 7.1, 7.2 Hz, 1H), 2.46 – 2.24 (m, 6H); ^{19}F NMR (282 MHz, dmso) δ -69.49 (s); LCMS $(M+H)^+$: 581.3

Example 61. {trans-3-(4-{[6-(1-aminocyclobutyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step A. Ethyl-4-cyclobutyl-4-hydroxy-2-oxobut-3-enoate

Ethanol (4.39 mL, 75.2 mmol) was added dropwise to a suspension of sodium hydride (0.607 g, 15.2 mmol, 60% in mineral oil) in a flask that was held in an ice bath.

Ten minutes after complete addition, a mixture of 1-cyclobutylethanone (1.5 mL, 14 mmol, Aldrich) and diethyl oxalate (2.01 g, 13.8 mmol, Aldrich) was added dropwise. After stirring overnight, 4.0 M sulfuric acid in water (0.00759 L, 30.4 mmol) was added. The product was extracted into diethyl ether. The combined organic extracts were washed with water and brine, dried over sodium sulfate, filtered and concentrated. The material was used without further purification in Step B.

Step B. Ethyl 6-cyclobutyl-2-(trifluoromethyl)pyrimidine-4-carboxylate

To a solution of 2,2,2-trifluoroethanimidamide (1.80 g, 13.6 mmol, Matrix) in ethanol (22 mL, 370 mmol) was added a solution of ethyl (3Z)-4-cyclobutyl-4-hydroxy-2-oxobut-3-enoate (2.7 g, 14 mmol, from Step A) in a small volume of ethanol. The solution was cooled in an ice bath and a solution of hydrogen chloride in ethanol (21 mL, 360 mmol, prepared by bubbling HCl gas through the ethanol for 10 minutes) was added. The reaction was allowed to warm to room temperature and stirred overnight. The mixture was added slowly to a saturated solution of sodium bicarbonate. Additional solid potassium carbonate was added. After neutralization was complete, ethanol was removed *in vacuo*. The product was extracted with three portions of DCM. The combined extracts were dried over sodium sulfate, filtered and evaporated. The product was purified by flash chromatography on silica gel, eluting with a gradient from 0-25% EtOAc/hexanes to afford a yellow oil (1.8 g, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 4.51 (q, J = 7.1 Hz, 2H), 3.81 (p, J = 8.6 Hz, 1H), 2.48 – 2.33 (m, 4H), 2.21 – 2.08 (m, 1H), 2.03 – 1.93 (m, 1H), 1.45 (t, J = 7.1 Hz, 3H); LCMS $(M+H)^+$: 275.1

Step C. 6-(1-Bromocyclobutyl)-2-(trifluoromethyl)pyrimidine-4-carboxylic acid

Bromine (0.13 mL, 2.6 mmol) was added to a solution of ethyl 6-cyclobutyl-2-(trifluoromethyl)pyrimidine-4-carboxylate (0.65 g, 2.4 mmol, from Step B) in acetic acid (2.0 mL) and the reaction was heated to 80 °C for one hour. The mixture was concentrated and the resulting oil was dissolved in THF (8.0 mL) and cooled to 0 °C. A solution of lithium hydroxide, monohydrate (0.20 g, 4.7 mmol) in water (2.0 mL) was added. After stirring for 20 minutes, 1N HCl was added to achieve pH 4. Additional

water was introduced and the product was extracted with six portions of 10% isopropanol in chloroform. The combined extracts were dried over sodium sulfate, filtered and concentrated to afford product which was used without further purification (0.64 g, 80%). ^{1}H NMR (400 MHz, dmso) δ 8.27 (s, 1H), 3.17 – 2.97 (m, 2H), 2.92 – 2.71 (m, 2H), 2.34 (dtt, *J* = 10.9, 9.1, 6.9 Hz, 1H), 1.84 (dtt, *J* = 11.0, 8.6, 5.6 Hz, 1H); LCMS $(M+H)^+$: 324.9, 326.7.

Step D. {trans-3-(4-{[6-(1-Bromocyclobutyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

Triethylamine (0.14 mL, 0.97 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.129 g, 0.292 mmol) were added to a solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.12 g, 0.24 mmol, from Step 1 of Example 1b) and 6-(1-bromocyclobutyl)-2-(trifluoromethyl)pyrimidine-4-carboxylic acid (0.095 g, 0.29 mmol, from Step C) in N,N-dimethylformamide (2.4 mL). After a reaction time of 1 hour, the mixture was diluted with EtOAc and washed with water (3x), followed by brine, dried over sodium sulfate, filtered and concentrated. Flash chromatography on silica gel, eluting with a gradient from 0-5% MeOH in EtOAc afforded product as an oil (0.068 g, 35%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.47 (s, 1H), 8.33 (s, 1H), 8.04 (s, 1H), 7.41 (d, *J* = 3.7 Hz, 1H), 6.81 (d, *J* = 3.7 Hz, 1H), 5.68 (s, 2H), 3.91 – 3.80 (m, 2H), 3.75 – 3.63 (m, 2H), 3.59 – 3.48 (m, 2H), 3.21 (s, 2H), 3.20-1.85 (m, 15H), 1.05 – 0.74 (m, 2H), -0.06 (s, 9H); LCMS $(M+H)^+$: 799.3, 801.2.

Step E. {trans-3-(4-{[6-(1-Aminocyclobutyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

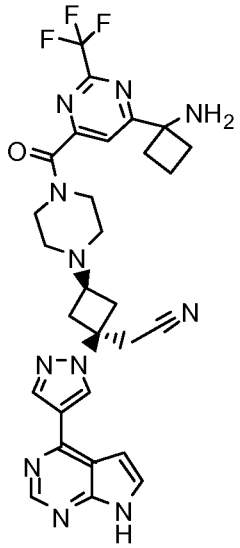
Sodium azide (16 mg, 0.24 mmol) was added to a solution of {trans-3-(4-{[6-(1-bromocyclobutyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7-

{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.065 g, 0.081 mmol, from Step D) in dimethyl sulfoxide (0.42 mL). After stirring for 4 hours, the reaction was worked up by partitioning between ethyl acetate and brine. The EtOAc layer was washed with additional brine, dried over sodium sulfate, filtered and concentrated. The resulting product was dissolved in THF (1.8 mL) and water (0.4 mL) and 1.0 M trimethylphosphine in THF (0.098 mL, 0.098 mmol) was added dropwise. After 20 minutes, the solvent was removed *in vacuo*, and the residue was purified by flash chromatography on silica gel, eluting with a gradient from 0-5% MeOH in DCM to afford product as an oil (14 mg, 24%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.46 (s, 1H), 8.33 (s, 1H), 8.03 (s, 1H), 7.41 (d, J = 3.7 Hz, 1H), 6.81 (d, J = 3.7 Hz, 1H), 5.68 (s, 2H), 3.93 – 3.79 (m, 2H), 3.72 – 3.57 (m, 2H), 3.21 (s, 2H), 3.12 – 2.79 (m, 3H), 2.75 – 2.57 (m, 2H), 2.56 – 2.37 (m, 6H), 2.30 – 2.10 (m, 3H), 2.05 – 1.90 (m, 1H), 1.01 – 0.77 (m, 2H), -0.06 (s, 9H); LCMS $(M+H)^+$: 736.3.

Step F. {trans-3-(4-{[6-(1-Aminocyclobutyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

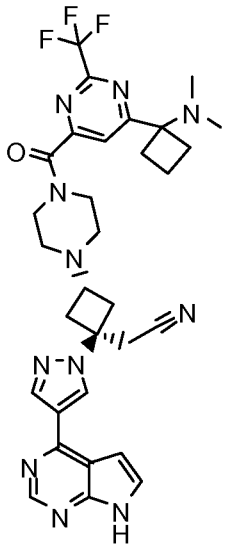
{trans-3-(4-{[6-(1-Aminocyclobutyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (14 mg, 0.019 mmol, from Step E) was stirred with 1:1 mixture of TFA:DCM for one hour and then solvents were removed *in vacuo*. The residue was dissolved in 0.5 mL MeOH, and 0.1 mL of ethylenediamine was added. Purification via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) afforded product as the free base (3.5 mg, 30%). ^{1}H NMR (400 MHz, dmso) δ 12.13 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 8.06 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 3.78 – 3.63 (m, 2H), 3.43 (s, 2H), 3.41 – 3.31 (m, 2H), 3.08 – 2.94 (m, 2H), 2.84 (tt, J = 7.2, 7.2 Hz, 1H), 2.59 – 2.51 (m, 2H), 2.46 – 2.24 (m, 6H), 2.14 – 1.97 (m, 3H), 1.92 – 1.77 (m, 1H). ^{19}F NMR (376 MHz, dmso) δ -69.41 (s); LCMS $(M+H)^+$: 606.2.

Example 62. {cis-3-(4-{[6-(1-aminocyclobutyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



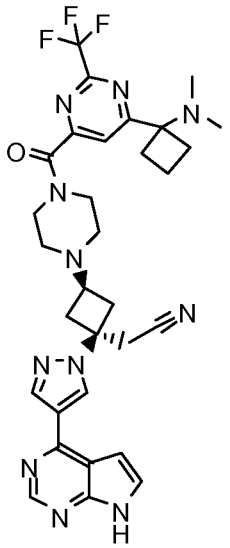
The title compound was prepared by the method of Example 61, using {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (from Step 9 of Example 1a). ^{1}H NMR (400 MHz, dmso) δ 12.12 (br s, 1H), 8.68 (s, 1H), 8.66 (s, 1H), 8.38 (s, 1H), 8.05 (s, 0H), 7.94 (s, 0H), 7.58 (d, J = 3.5 Hz, 1H), 7.04 (d, J = 3.6 Hz, 1H), 3.76 – 3.57 (m, 2H), 3.45 (s, 2H), 3.40 – 3.19 (m, 2H), 2.95 (tt, J = 7.6, 7.9 Hz, 1H), 2.72 – 2.45 (m, 7H), 2.44 – 2.34 (m, 2H), 2.34 – 2.24 (m, 2H), 2.13 – 1.91 (m, 1H), 1.95 – 1.68 (m, 1H), 1.32 – 1.18 (m, 1H), 1.18 – 1.05 (m, 1H); LCMS $(M+H)^+$: 606.2.

Example 63. {trans-3-(4-{[6-[1-(dimethylamino)cyclobutyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



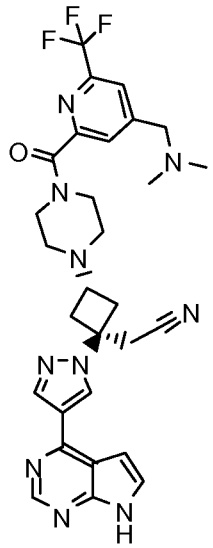
{trans-3-(4-{[6-(1-Aminocyclobutyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (15 mg, 0.020 mmol, Example 61, Step E) was dissolved in methanol (0.86 mL, 21 mmol), and acetic acid (0.013 mL, 0.22 mmol), sodium cyanoborohydride (7.7 mg, 0.12 mmol) and 37 wt% formaldehyde in water (5.4 mg, 0.066 mmol, Sigma-Aldrich) were added. After 20 minutes, the mixture was concentrated. The residue was stirred in a solution of TFA:DCM (1:1) for one hour and concentrated again. The residue was dissolved in 0.5 mL MeOH to which 100 μL ethylenediamine was added, and stirred until deprotection was complete. Purification via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) afforded product as the free base (5.3 mg, 40%). ^{1}H NMR (400 MHz, dmso) δ 12.12 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.89 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 3.84 – 3.61 (m, 2H), 3.43 (s, 2H), 3.41 – 3.36 (m, 2H), 3.07 – 2.97 (m, 2H), 2.85 (tt, J = 7.2, 7.2 Hz, 1H), 2.48 – 2.19 (m, 10H), 1.96 (s, 6H), 1.88 – 1.73 (m, 1H), 1.65 – 1.49 (m, 1H); ^{19}F NMR (376 MHz, dmso) δ -69.52 (s); LCMS $(M+H)^+$: 634.2.

Example 64. {cis-3-(4-{[6-[1-(dimethylamino)cyclobutyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



The title compound was prepared in the manner of Example 63 starting with the product of Example 62 (22 mg, 0.030 mmol) to afford purified product (7.4 mg, 33%). ^{1}H NMR (400 MHz, dmso) δ 12.17 (br s, 1H), 8.68 (s, 1H), 8.66 (s, 1H), 8.38 (s, 1H), 7.88 (s, 1H), 7.58 (d, J = 3.6 Hz, 1H), 7.04 (d, J = 3.6 Hz, 1H), 3.72 – 3.60 (m, 2H), 3.45 (s, 2H), 3.41 – 3.00 (m, 2H), 2.95 (tt, J = 7.4, 7.6 Hz, 1H), 2.76 – 2.16 (m, 12H), 1.94 (s, 6H), 1.86 – 1.68 (m, 1H), 1.64 – 1.46 (m, 1H); ^{19}F NMR (376 MHz, dmso) δ -69.53 (s), -73.86 (s); LCMS $(M+H)^+$: 597.0

Example 65. {trans-3-(4-{[4-[(dimethylamino)methyl]-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step A. 6-(Trifluoromethyl)-4-vinylpyridine-2-carboxylic acid

A mixture of 4-bromo-6-(trifluoromethyl)pyridine-2-carboxylic acid (0.50 g, 1.8 mmol, Anichem), (2-Ethenyl)tri-n-butyltin (919 μL, 3.14 mmol, Aldrich) and tetrakis(triphenylphosphine)palladium(0) (428 mg, 0.370 mmol, Strem) in toluene (4.2 mL) was degassed by a stream of nitrogen through the solution for 15 minutes. Triethylamine (774 μL, 5.56 mmol) was added and the mixture was heated to 80°C for 2 hours. After cooling to ambient temperature, water and 1N NaOH were added and the product was extracted with four portions of ethyl acetate. The aqueous layer was then treated with 1N HCl to achieve a pH between 4 and 5, and was extracted with six portions of 10% isopropanol in chloroform. The combined organic extracts were dried over sodium sulfate, filtered and concentrated to afford crude product, which was used without further purification in Step B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, J = 1.3 Hz, 1H), 7.88 (d, J = 1.5 Hz, 1H), 6.82 (dd, J = 17.6, 10.9 Hz, 1H), 6.23 (d, J = 17.4 Hz, 1H), 5.78 (d, J = 10.9 Hz, 1H); LCMS $(M+H)^+$: 218.1.

Step B. 4-formyl-6-(trifluoromethyl)pyridine-2-carboxylic acid

6-(Trifluoromethyl)-4-vinylpyridine-2-carboxylic acid (0.30 g, 0.69 mmol, the crude product from Step A) was dissolved in 1,4-dioxane (20. mL) and water (5.0 mL), then sodium periodate (0.44 g, 2.1 mmol, Aldrich) was added, followed by 4 wt% osmium tetraoxide in water (0.152 mL, 0.0240 mmol, Aldrich). The reaction was stirred

overnight. Sodium thiosulfate solution was added and the mixture was stirred for 30 minutes. 1N HCl was added to adjust the pH to between 4 and 5, and the product was extracted with ten portions of 10% isopropanol in $CHCl_3$. The combined extracts were dried over sodium sulfate, filtered and concentrated. Flash chromatography on silica gel, eluting with a gradient from 0-10% MeOH in DCM afforded a partially purified product (94 mg, 20% yield over Steps A & B). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.25 (s, 1H), 8.83 (d, J = 0.8 Hz, 1H), 8.38 (d, J = 1.3 Hz, 1H).

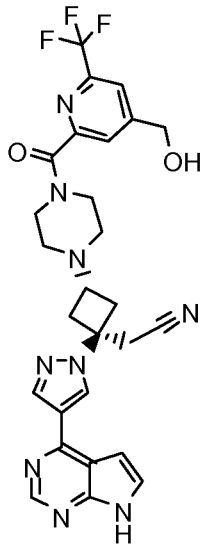
Step C. {trans-3-(4-{[4-Formyl-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

Triethylamine (0.095 mL, 0.68 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (0.14 g, 0.31 mmol) were added to a solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.15 g, 0.31 mmol, from Step 1 of Example 1b) and 4-formyl-6-(trifluoromethyl)pyridine-2-carboxylic acid (90 mg, 0.2 mmol, from Step B) in N,N-dimethylformamide (1.7 mL). After stirring for 30 minutes, the mixture was diluted with EtOAc and was washed with water (3x), followed by brine, then dried over sodium sulfate, filtered and concentrated. Flash chromatography on silica gel, eluting with a gradient from 0-10% MeOH in DCM afforded product as a light yellow solid (52 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.85 (s, 1H), 8.47 (s, 1H), 8.38 (s, 1H), 8.33 (s, 1H), 8.15 (d, J = 1.3 Hz, 1H), 7.41 (d, J = 3.7 Hz, 1H), 6.81 (d, J = 3.7 Hz, 1H), 5.68 (s, 2H), 3.96 – 3.81 (m, 2H), 3.79 – 3.59 (m, 2H), 3.59 – 3.49 (m, 2H), 3.21 (s, 2H), 3.09 – 3.01 (m, 2H), 2.97 (tt, J = 6.3, 6.7 Hz, 1H), 2.57 – 2.38 (m, 6H), 0.95 – 0.86 (m, 2H), -0.06 (s, 9H); LCMS $(M+H)^+$: 694.2.

Step D. {trans-3-(4-{[4-[(Dimethylamino)methyl]-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

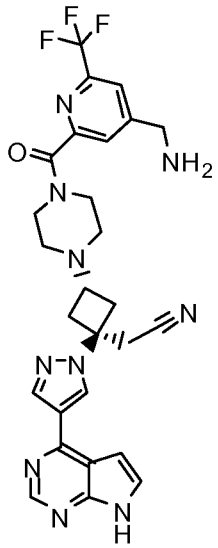
2.0 M Dimethylamine in THF (130 μL, 0.26 mmol, Aldrich) and sodium triacetoxyborohydride (27 mg, 0.129 mmol) were added to a solution of {trans-3-(4-{[4-formyl-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (15 mg, 0.022 mmol, from Step C) in methylene chloride (1.0 mL) and the reaction was stirred overnight. The mixture was concentrated, then the solvent was replaced with isopropyl alcohol (0.50 mL). This was followed by the addition of 2.0 M dimethylamine in THF (22 μL, 0.043 mmol) and excess sodium triacetoxyborohydride. After stirring for 24 hours, 0.1 N NaOH was added and the product was extracted with EtOAc. The combined extracts were washed twice with water, once with brine, dried over sodium sulfate, filtered and concentrated. The residue was stirred in a 1:1 mixture of DCM:TFA for one hour, was concentrated, then was redissolved in 1 mL methanol to which 0.15 mL ethylenediamine was subsequently added. Purification via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) afforded product as the free base (2.0 mg, 16%). ^1H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.89 (d, J = 1.3 Hz, 1H), 7.82 (s, 1H), 7.51 (d, J = 3.6 Hz, 1H), 6.99 (d, J = 3.6 Hz, 1H), 3.91 – 3.81 (m, 2H), 3.64 (s, 2H), 3.60 – 3.55 (m, 2H), 3.35 (s, 2H), 3.11 – 3.04 (m, 2H), 2.97 (tt, J = 6.9, 7.1 Hz, 1H), 2.62 – 2.38 (m, 6H), 2.28 (s, 6H); ^{19}F NMR (376 MHz, CD_3OD) δ -71.39 (s); LCMS $(M+H)^+$: 593.2

Example 66. {trans-3-(4-{[4-(hydroxymethyl)-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Example 66 was obtained as a byproduct in the reaction of Example 65, Step D and was isolated during the HPLC purification as described above in that Example (2.5 mg, 20%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.72 (s, 1H), 8.67 (s, 1H), 8.40 (s, 1H), 7.88 (d, J = 1.4 Hz, 1H), 7.82 (s, 1H), 7.51 (d, J = 3.6 Hz, 1H), 6.99 (d, J = 3.6 Hz, 1H), 4.78 (s, 2H), 3.92 – 3.73 (m, 2H), 3.63 – 3.49 (m, 2H), 3.35 (s, 2H), 3.15 – 3.02 (m, 2H), 2.97 (tt, J = 6.7, 6.9 Hz, 1H), 2.64 – 2.36 (m, 6H); ^{19}F NMR (376 MHz, CD_3OD) δ -69.84 (s); LCMS $(M+H)^+$: 566.2.

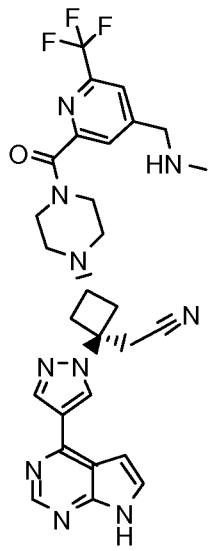
Example 67. {trans-3-(4-{[4-(aminomethyl)-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



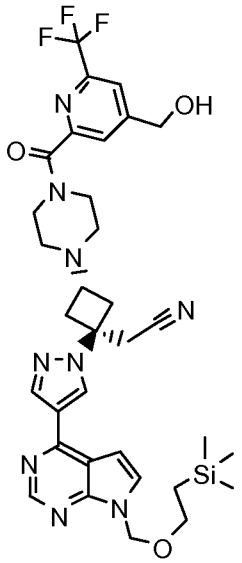
Triethylamine (6.0 μL, 0.043 mmol) and methanesulfonyl chloride (2.2 μL, 0.028 mmol) were added to a solution of {trans-3-(4-{[4-(hydroxymethyl)-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (15 mg, 0.022 mmol, prepared as described in Example 68, Step A) in methylene chloride (0.75 mL). After 15 minutes, solvent was removed *in vacuo* and 7.0 M ammonia in methanol (0.3 mL, 2 mmol, Aldrich) was introduced. After 3.5 hours, the mixture was concentrated, the residue was dissolved in a 1:1 mixture of TFA:DCM, stirred for one hour, then concentrated again. The residue was redissolved in 1 mL MeOH, and 0.2 ml ethylenediamine was then added. When deprotection was complete, the product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH), affording product as the free base (2.0 mg, 16%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.95 – 7.87 (m, 1H), 7.82 (s, 1H), 7.51 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 3.96 (s, 2H), 3.92 – 3.80 (m, 2H), 3.61 – 3.53 (m, 2H), 3.35 (s, 2H), 3.14 – 3.02 (m, 2H), 2.97 (tt, J = 6.9, 7.0 Hz, 1H), 2.61 – 2.40 (m, 6H); ^{19}F NMR (376 MHz, CD_3OD) δ -69.78 (s); LCMS $(M+H)^+$: 565.3

Example 68. {trans-3-(4-{[4-[(methylamino)methyl]-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-

yl]cyclobutyl}acetonitrile



Step A. {trans-3-(4-{[4-(Hydroxymethyl)-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



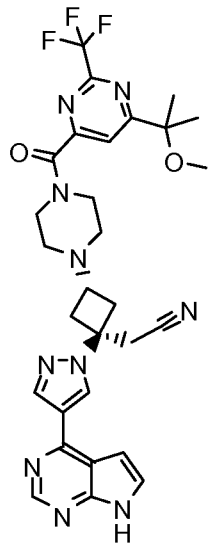
Sodium tetrahydroborate (1.7 mg, 0.046 mmol) was added to a solution of {trans-3-(4-{[4-formyl-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (32 mg, 0.046 mmol, Example 65, Step C) in ethanol (0.50 mL). After 30 minutes, the reaction was diluted with water and the product was extracted

with EtOAc. The combined extracts were washed with water (3x), followed by brine, dried over sodium sulfate, filtered and concentrated to afford a near theoretical yield of product, used without further purification in Step B. LCMS $(M+H)^+$: 696.3.

Step B. {trans-3-(4-{[4-[(Methylamino)methyl]-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

Triethylamine (4.8 μL, 0.034 mmol) and methanesulfonyl chloride (1.7 μL, 0.022 mmol) were added to a solution of {trans-3-(4-{[4-(hydroxymethyl)-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (12 mg, 0.017 mmol, from Step B) in methylene chloride (0.60 mL). After 15 minutes, solvent was removed *in vacuo* and methylamine 33 wt% in ethanol (50 mg, 0.5 mmol, Aldrich) was added. The reaction was continued for 1.5 hours, then solvent was again removed *in vacuo*. The crude product was dissolved in a 1:1 mixture of TFA:DCM, stirred for one hour, then concentrated again. The residue was redissolved in 1 mL of MeOH, and 0.2 mL ethylenediamine was added. When deprotection was determined complete by LCMS, the product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) to afford product as the free base (3.9 mg , 39%). ^1H NMR (300 MHz, dmso) δ 12.11 (br s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.41 (s, 1H), 7.93 (d, J = 1.3 Hz, 1H), 7.81 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 3.81 (s, 2H), 3.76 – 3.63 (m, 2H), 3.43 (s, 2H), 3.41 – 3.36 (m, 2H), 3.08 – 2.94 (m, 2H), 2.84 (tt, J = 7.0, 7.0 Hz, 1H), 2.45 – 2.27 (m, 6H), 2.26 (s, 3H); ^{19}F NMR (282 MHz, dmso) δ -66.83 (s); LCMS $(M+H)^+$: 579.2

Example 69. {trans-3-(4-{[6-(1-methoxy-1-methylethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step A. 6-(1-Methoxy-1-methylethyl)-2-(trifluoromethyl)pyrimidine-4-carboxylic acid

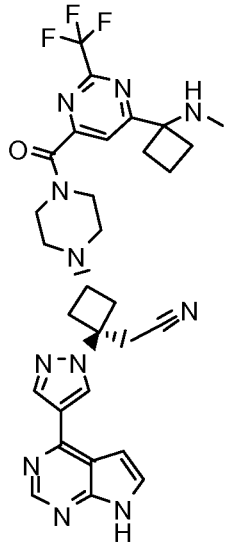
Sodium hydride (0.032 g, 0.80 mmol, 60% in mineral oil) and methyl iodide (0.031 mL, 0.50 mmol) were added to a solution of 6-(1-hydroxy-1-methylethyl)-2-(trifluoromethyl)pyrimidine-4-carboxylic acid (0.050 g, 0.20 mmol, Example 58, Step B) in N,N-dimethylformamide (1 mL, 10 mmol). After stirring overnight, water and lithium hydroxide monohydrate (0.050 g, 1.2 mmol) were added into the reaction. After stirring for 1.5 hours, the reaction was acidified by the addition of 1 N HCl to achieve pH between 3 and 4. The product was extracted with ethyl acetate (3x). The combined extracts were dried over sodium sulfate, filtered and concentrated. The residue was dissolved and rotovapped twice with MeOH to afford product which was used without further purification (0.045 g, 85%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 3.29 (s, 3H), 1.56 (s, 6H); LCMS $(M+H)^+$: 265.1

Step B. {trans-3-(4-{[6-(1-Methoxy-1-methylethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

To a solution of 6-(1-methoxy-1-methylethyl)-2-(trifluoromethyl)pyrimidine-4-carboxylic acid (0.045 g, 0.17 mmol, from Step A) in N,N-dimethylformamide (4 mL) was added, sequentially, a solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-

(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.0852 g, 0.173 mmol, from Step 1 of Example 1b) in N,N-dimethylformamide (2.5 mL), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (90.4 mg, 0.204 mmol) and triethylamine (0.12 mL, 0.85 mmol). After stirring overnight, the reaction was worked up by partition between ethyl acetate and brine, and the aqueous layer was extracted with a further two portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and concentrated. The product was deprotected by stirring with TFA:DCM 1:1 for 1 hour, evaporating and stirring with excess ethylenediamine in methanol overnight. The solution was filtered and purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH), frozen and lyophilized to afford product as the free base (0.03 g, 30%). ^1H NMR (300 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.84 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 8.06 (s, 1H), 7.40 (dd, J = 3.7, 2.2 Hz, 1H), 6.81 (dd, J = 3.7, 1.8 Hz, 1H), 3.95 – 3.71 (m, 2H), 3.71 – 3.55 (m, 1H), 3.29 (s, 3H), 3.21 (s, 2H), 3.10 – 2.87 (m, 3H), 2.57 – 2.30 (m, 6H), 1.56 (s, 6H); LCMS $(M+H)^+$: 609.3

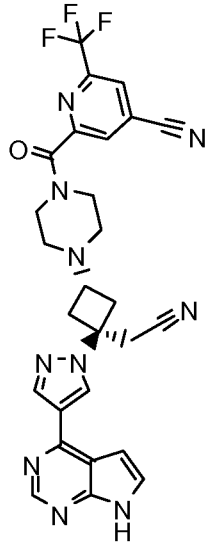
Example 70. {trans-3-(4-{[6-[1-(methylamino)cyclobutyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



To 1H-benzotriazole-1-methanol (3.0 mg, 0.020 mmol, Aldrich) in ethanol (0.30

mL) was added {trans-3-(4-{[6-(1-aminocyclobutyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (15 mg, 0.020 mmol, Example 61, Step E). The solution was heated to 78 °C in a sealed vial for one hour. After cooling to room temperature, solvent was removed *in vacuo* and the residue was dissolved in tetrahydrofuran (0.60 mL). Sodium tetrahydroborate (4.6 mg, 0.12 mmol) was added and the mixture was stirred for 40 minutes before solvent was removed *in vacuo* again. The residue was redissolved in 2.0 mL of DCM and 0.40 mL of TFA was added dropwise. After stirring for 1.5 hours, the mixture was concentrated by rotary evaporation. Following this, the residue was stirred with ethylenediamine (0.10 mL) in MeOH (1.0 mL). When deprotection was complete, the product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) to afford the free base (2.0 mg, 16%). LCMS $(M+H)^+$: 620.4

Example 71. 2-[(4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)carbonyl]-6-(trifluoromethyl)isonicotinonitrile



Step A. 4-Cyano-6-(trifluoromethyl)pyridine-2-carboxylic acid

4-Bromo-6-(trifluoromethyl)pyridine-2-carboxylic acid (0.150 g, 0.556 mmol, Anichem) and zinc cyanide (0.39 g, 3.3 mmol) were mixed in N-methylpyrrolidinone (2

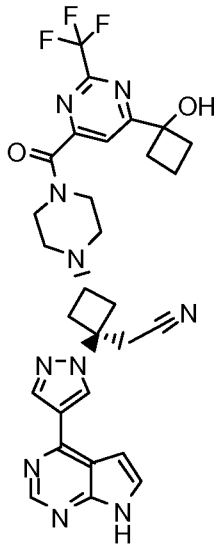
mL) and the mixture was degassed by bubbling a stream of nitrogen through the mixture for 10 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.096 g, 0.083 mmol) was added, the degassing was continued for 5 minutes, then the reaction was sealed and heated in the microwave to a temperature of 160 °C for 15 minutes. The mixture was filtered and purified by preparative HPLC (eluting with a gradient from 18.8 to 40.9% MeCN/H_2O containing 0.1% TFA over 1-6 min at 60 mL/min thru C18 SunFire 30 x 100 mm, 5 um particle size) using UV detection. The product eluted at 5.25 minutes.

Step B. 2-[(4-{trans-3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)carbonyl]-6-(trifluoromethyl)isonicotinonitrile

4-Cyano-6-(trifluoromethyl)pyridine-2-carboxylic acid (0.025 g, 0.12 mmol, from Step A) was dissolved in N,N-dimethylformamide (3 mL) and to this was added sequentially{trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.0579 g, 0.117 mmol, from Step 1 of Example 1b) as a solution in N,N-dimethylformamide (1.7 mL), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (61.4 mg, 0.139 mmol) and triethylamine (0.081 mL, 0.58 mmol). After stirring overnight, the reaction was worked up by partition between ethyl acetate and brine. The layers were separated and the aqueous was extracted with two further portions of ethyl acetate. The combined extracts were dried over sodium sulfate, filtered and concentrated. The SEM-protected intermediate was purified by flash chromatography on silica gel, eluting with a gradient of up to 100% EtOAc in Hexanes then 10-15% MeOH in DCM. A third of the material obtained was stirred with TFA:DCM 1:1 for 1 hour, evaporated, then stirred with 0.2 mL ethylenediamine in methanol for 30 minutes. The solution was then filtered and purified purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH), frozen and lyophilized to afford product as the free base (5 mg, 20%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 8.33 (d, J = 1.3 Hz, 1H), 8.26 (d, J = 1.1 Hz, 1H), 7.51 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 3.7 Hz, 1H), 3.89 – 3.80 (m, 2H), 3.62 – 3.53 (m, 2H), 3.35 (s, 2H), 3.12 – 3.03 (m, 2H), 2.97 (tt, J = 7.1, 7.3 Hz, 1H), 2.67 – 2.29 (m, 6H); ^{19}F NMR (376 MHz,

CD_3OD) δ -70.18 (s); LCMS $(M+H)^+$: 561.0

Example 72. {trans-3-(4-{[6-(1-hydroxycyclobutyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step A. 6-(1-Hydroxycyclobutyl)-2-(trifluoromethyl)pyrimidine-4-carboxylic acid

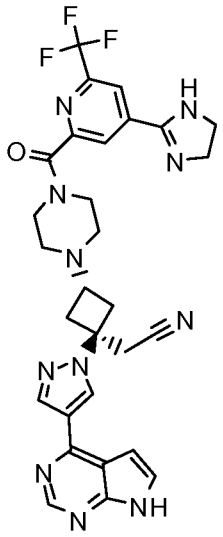
To a solution of ethyl 6-cyclobutyl-2-(trifluoromethyl)pyrimidine-4-carboxylate (0.200 g, 0.729 mmol, Example 61, Step B) in Water (1 mL) and *tert*-butyl alcohol (1 mL) was added potassium permanganate (0.23 g, 1.4 mmol) followed quickly by sodium carbonate (0.15 g, 1.4 mmol). After stirring overnight, the mixture was filtered. The resulting mixture stood open to the air for a period of 3 days, during which time a brown precipitate formed. The mixture was filtered again and purified via preparative HPLC-MS (C18 eluting with a gradient of $MeCN/H_2O$ containing 0.1% TFA) and evaporated to afford product with only a small amount of TFA present (0.01 g, 5%). ^1H NMR (300 MHz, CD_3OD) δ 8.41 (s, 1H), 2.75 – 2.46 (m, 2H), 2.44 – 2.15 (m, 2H), 2.18 – 1.77 (m, 2H); ^{19}F NMR (282 MHz, CD_3OD) δ -72.09 (s); LCMS $(M+H)^+$: 263.0

Step B. {trans-3-(4-{[6-(1-Hydroxycyclobutyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-

yl]cyclobutyl}acetonitrile

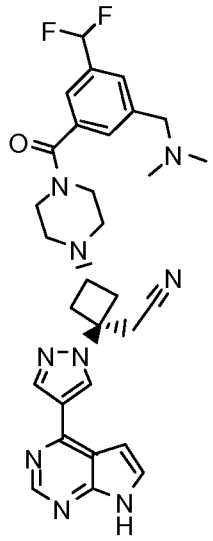
To 6-(1-hydroxycyclobutyl)-2-(trifluoromethyl)pyrimidine-4-carboxylic acid (0.010 g, 0.038 mmol, from Step A) and {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.019 g, 0.038 mmol, from Step 1 of Example 1b) in N,N-dimethylformamide (1 mL) was added benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (20.2 mg, 0.0458 mmol) and triethylamine (0.026 mL, 0.19 mmol). After stirring overnight, the reaction mixture was partitioned between water and ethyl acetate. The layers were separated and the aqueous was extracted with two further portions of ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, decanted and concentrated. Deprotection was carried out by stirring with 1:1 TFA:DCM for 1 hour, evaporating, then stirring with ethylenediamine (0.2 mL) in methanol until deprotection was complete. The product was purified via preparative HPLC-MS (C18 eluting with a gradient of $MeCN/H_2O$ containing 0.15% NH_4OH), frozen and lyophilized to afford product as the free base (15 mg, 65%). ^1H NMR (500 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.84 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 8.09 (s, 1H), 7.40 (dd, J = 3.7, 2.3 Hz, 1H), 6.81 (dd, J = 3.7, 1.8 Hz, 1H), 3.92 – 3.75 (m, 2H), 3.70 – 3.64 (m, 2H), 3.64 (s, 1H), 3.21 (s, 2H), 3.10 – 3.01 (m, 2H), 2.98 (tt, J = 6.7, 6.7 Hz, 1H), 2.69 – 2.57 (m, 2H), 2.57 – 2.37 (m, 8H), 2.20 – 1.93 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -70.72 (s); LCMS $(M+H)^+$: 607.2

Example 73. {trans-3-(4-{[4-(4,5-dihydro-1H-imidazol-2-yl)-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



The procedure of Example 71 was followed, with the modification that during the deprotection, stirring with ethylenediamine was continued overnight rather than for 30 minutes. ^{1}H NMR (300 MHz, dmso) δ 12.11 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 8.28 (d, J = 1.4 Hz, 1H), 8.21 (d, J = 1.1 Hz, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.46 (s, 1H), 7.07 (d, J = 3.6 Hz, 1H), 3.89 (t, J = 10.1 Hz, 2H), 3.77 – 3.61 (m, 2H), 3.49 (t, J = 10.4 Hz, 2H), 3.44 – 3.36 (m, 4H), 3.07 – 2.96 (m, 2H), 2.84 (tt, J = 6.8, 7.0 Hz, 1H), 2.47 – 2.14 (m, 6H); ^{19}F NMR (282 MHz, dmso) δ -67.02 (s); LCMS $(M+H)^+$: 604.3

Example 74. {trans-3-(4-{3-(difluoromethyl)-5-[(dimethylamino)methyl]benzoyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step A. Methyl 3-[(dimethylamino)methyl]-5-(hydroxymethyl)benzoate

To a reaction vial was added methyl 3-bromo-5-(hydroxymethyl)benzoate (1.2 g, 4.9 mmol, prepared as described in WO 2003/048111 from dimethyl 5-bromoisophthalate, Alfa Aesar), cesium carbonate (4.79 g, 14.7 mmol), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (280 mg, 0.59 mmol, Aldrich), potassium [(dimethylamino)methyl](trifluoro)borate(1-) (0.970 g, 5.88 mmol, Aldrich), palladium acetate (66 mg, 0.29 mmol) and THF:H_2O (10:1, 30 mL). The reaction mixture was degassed by purging with a stream of nitrogen for 10 minutes. The vial was sealed and heated at 80 °C for 17 hours. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was was washed twice with water. The combined aqueous portions were then saturated with NaCl, and the product was extracted with eight portions of DCM. The extracts were dried over sodium sulfate, filtered and concentrated to afford product as a colorless oil (0.37 g, 34%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.88 (s, 1H), 7.56 (s, 1H), 4.74 (s, 2H), 3.91 (s, 3H), 3.46 (s, 2H), 2.24 (s, 6H); LCMS $(M+H)^+$: 224.1.

Step B. Methyl 3-[(dimethylamino)methyl]-5-formylbenzoate

Manganese(IV) oxide (0.72 g, 8.3 mmol) was added to methyl 3-[(dimethylamino)methyl]-5-(hydroxymethyl)benzoate (0.37 g, 1.6 mmol, from Step A) in toluene (15 mL). The mixture was heated to 105 °C for 2 hours, then was cooled to

room temperature and filtered. Solvent was removed from the filtrate *in vacuo* to afford the product as a colorless oil (0.30 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.07 (s, 1H), 8.43 (dd, 1H), 8.25 (dd, 1H), 8.05 (dd, 1H), 3.96 (s, 3H), 3.54 (s, 2H), 2.26 (s, 6H); LCMS $(M+H)^+$: 222.1.

Step C. Methyl 3-(difluoromethyl)-5-[(dimethylamino)methyl]benzoate

Methyl 3-[(dimethylamino)methyl]-5-formylbenzoate (99 mg, 0.45 mmol, from Step B), was stirred in deoxoFluor® (495 μL, 2.69 mmol) containing ethanol (5 μL, 0.09 mmol) for 24 hours. The mixture was quenched by dropwise addition into ice-cold saturated $NaHCO_3$ solution. The product was isolated by extraction using DCM. The organic extract was washed twice with water, once with brine, was dried over sodium sulfate, filtered and concentrated to afford product as a light yellow oil which was used without further purification (0.046 g, 30%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 2H), 7.69 (s, 1H), 6.68 (t, 1H), 3.94 (s, 3H), 3.36 (s, 2H), 2.25 (s, 6H); LCMS $(M+H)^+$: 244.1.

Step D. 3-(Difluoromethyl)-5-[(dimethylamino)methyl]benzoic acid

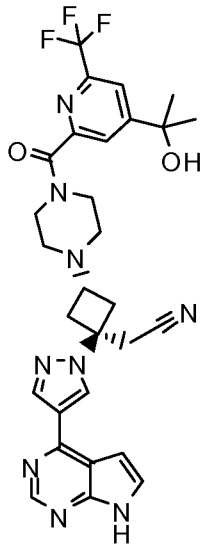
Lithium hydroxide, monohydrate (65.2 mg, 1.55 mmol) in water (0.7 mL) was added to a solution of methyl 3-(difluoromethyl)-5-[(dimethylamino)methyl]benzoate (45 mg, 0.13 mmol, from Step C) in tetrahydrofuran (2 mL). Upon stirring for 3.5 hours, the mixture was treated with 1N HCl to adjust the pH to 7, then THF was removed by rotary evaporation. Acetonitrile was added to make a 1:1 ACN:water mixture, the mixture was filtered, and the filtrate was purified via preparative HPLC-MS (C18 eluting with a gradient of $MeCN/H_2O$ containing 0.15% NH_4OH) to afford product as a white solid (0.030 g, 100%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.95 (s, 2H), 7.50 (s, 1H), 7.05 (t, 1H), 3.44 (s, 2H), 2.15 (s, 6H); LCMS $(M+H)^+$: 230.1.

Step E. {trans-3-(4-{3-(Difluoromethyl)-5-[(dimethylamino)methyl]benzoyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

3-(Difluoromethyl)-5-[(dimethylamino)methyl]benzoic acid (14.0 mg, 0.0609

mmol, from Step D) was dissolved in THF (0.56 mL). Triethylamine (28.3 μL, 0.203 mmol) and N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (21.2 mg, 0.0558 mmol) were added and the mixture was stirred for 15 minutes. {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (25.0 mg, 0.0507 mmol, from Step 1 of Example 1b) was added, and the reaction was stirred for two hours. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with water, 0.1N NaOH and sat. NaCl, dried over sodium sulfate, filtered and concentrated. The residue was dissolved in a 1:1 mixture of DCM:TFA, stirred for 1 hour, concentrated again, then stirred with ethylenediamine (0.2 mL) in Methanol (1 mL) until deprotection was complete. The product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH), frozen and lyophilized to afford the free base (11.8 mg, 40%). ^{1}H NMR (400 MHz, dmso) δ 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, J = 3.5 Hz, 1H), 7.58 (s, 1H), 7.45 (s, 2H), 7.26 – 6.77 (m, 2H), 3.66 (br m, 2H), 3.47 (s, 2H), 3.43 (s, 2H), 3.34 (br m, 2H), 3.07 – 2.89 (m, 2H), 2.83 (tt, J = 7.3, 7.4 Hz, 1H), 2.43 – 2.21 (m, 6H), 2.15 (s, 6H); ^{19}F NMR (376 MHz, dmso) δ -107.70 (d, J = 55.9 Hz); LCMS $(M+H)^+$: 574.3.

Example 75. {trans-3-(4-{[4-(1-hydroxy-1-methylethyl)-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step A. 2-Chloro-6-(trifluoromethyl)isonicotinic acid and 2-chloro-6-(trifluoromethyl)nicotinic acid

2-Chloro-6-(trifluoromethyl)pyridine (20.0 g, 110 mmol, Synquest) was dissolved in tetrahydrofuran (400 mL) and then 1.0 M lithium chloride - chloro(2,2,6,6-tetramethylpiperidin-1-yl)magnesium (1:1) in THF (132 mL, 132 mmol, Aldrich) was added. The reaction was stirred at room temperature for 1 hour and was then cooled to -78 °C, and 67 g of solid dry ice was added into the flask. The reaction was stirred at -78 °C for 1 hour and subsequently allowed to slowly warm to room temperature. Upon reaching room temperature, the reaction was quenched with water, and was poured into 1N NaOH and washed with diethyl ether. The aqueous phase was then acidified with c.HCl to pH~ 1 and extracted with diethyl ether. The combined extracts were washed with water, then sat'd NaCl, dried over Na_2SO_4, filtered concentrated to afford a 1.2:1 regioisomeric mixture of carboxylic acids (11.65 g, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, J = 7.9, 0.8 Hz, 1H), 8.17 (d, J = 1.1 Hz, 1H), 8.11 (dd, J = 1.1, 0.6 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H).

Step B. 2-[2-Chloro-6-(trifluoromethyl)pyridin-4-yl]propan-2-ol (desired isomer isolated)

To a solution of 2-chloro-6-(trifluoromethyl)nicotinic acid (0.45 g, 2.0 mmol) and 2-chloro-6-(trifluoromethyl)isonicotinic acid (0.55 g, 2.4 mmol) (as a mixture from Step

A) in tetrahydrofuran (10 mL) cooled in an ice bath was added triethylamine (0.64 mL, 4.6 mmol) followed by isobutyl chloroformate (0.60 mL, 4.6 mmol, Aldrich). The reaction was stirred for 30 minutes, then was filtered through a pad of celite into a flask containing 3.0 M methylmagnesium bromide in diethyl ether (4.0 mL, 12 mmol, Aldrich) in tetrahydrofuran (5 mL) also cooled in an ice bath. The celite pad was rinsed with an additional 10 mL of THF. After warming to room temperature, an additional portion of 3.0 M methylmagnesium bromide in diethyl ether (4.0 mL, 12 mmol) was added to the reaction mixture. When the reaction was determined to be complete by LCMS, saturated ammonium chloride solution was added to the reaction. After stirring for 20 minutes, the mixture was transferred to a separatory funnel and was extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over sodium sulfate, filtered and concentrated. Flash chromatography on silica gel, eluting with a gradient from 0-30% EtOAc/Hexanes afforded product (0.28 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 1.4 Hz, 1H), 7.63 (d, J = 1.2 Hz, 1H), 1.60 (s, 6H); LCMS $(M+H)^+$: 240.1, 242.1.

Step C. 4-(1-Hydroxy-1-methylethyl)-6-(trifluoromethyl)pyridine-2-carbonitrile

A solution of 2-[2-chloro-6-(trifluoromethyl)pyridin-4-yl]propan-2-ol (0.230 g, 0.960 mmol, from Step B) and zinc cyanide (0.676 g, 5.76 mmol) in N-methylpyrrolidinone (4 mL) was degassed by bubbling a stream of nitrogen through the solution for 10 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.22 g, 0.19 mmol) was added and degassed similarly for 5 additional minutes. The vial was sealed and heated in the microwave to 140 °C for 10 minutes. The reaction mixture was worked up by partitioning between water and ethyl acetate, extracting (3x), and drying the combined extracts over sodium sulfate. The dried extract was then filtered and concentrated. Flash chromatography on silica gel, eluting with a gradient from 0-25% EtOAc/Hexanes afforded product (110 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 1.5 Hz, 1H), 7.99 (d, J = 1.6 Hz, 1H), 1.62 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -68.39 (s); LCMS $(M+H)^+$: 231.1.

Step D. 4-(1-Hydroxy-1-methylethyl)-6-(trifluoromethyl)pyridine-2-carboxylic acid

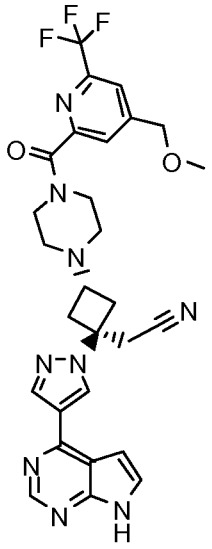
To a solution of 4-(1-hydroxy-1-methylethyl)-6-(trifluoromethyl)pyridine-2-carbonitrile (0.088 g, 0.38 mmol, from Step C) in ethanol (4 mL) was added 1.0 M sodium hydroxide in water (1.5 mL, 1.5 mmol) and the reaction was heated to 90 °C for 20 minutes. Upon cooling to room temperature, the reaction was acidified by the addition of 1 N HCl to achieve pH 5 and the ethanol was removed *in vacuo*. The remaining aqueous mixture was extracted with ethyl acetate (3x). The combined extracts were dried over sodium sulfate, decanted and concentrated to afford product, used without further purification (80 mg, 84%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (d, J = 1.6 Hz, 1H), 8.10 (d, J = 1.6 Hz, 1H), 1.57 (s, 6H); ^{19}F NMR (376 MHz, CD_3OD) δ -69.39 (s); LCMS $(M+H)^+$: 250.1.

Step E. {trans-3-(4-{[4-(1-Hydroxy-1-methylethyl)-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

4-(1-Hydroxy-1-methylethyl)-6-(trifluoromethyl)pyridine-2-carboxylic acid (0.0498 g, 0.200 mmol, from Step D) was dissolved in N,N-dimethylformamide (5 mL) and to this was added {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.100 g, 0.203 mmol, from Step 1 of Example 1b), followed by benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (106.1 mg, 0.2398 mmol) and triethylamine (0.14 mL, 1.0 mmol). The reaction was stirred overnight, then was partitioned between ethyl acetate and brine. The aqueous portion was extracted with two further portions of ethyl acetate. The combined extracts were dried over sodium sulfate, filtered and concentrated. The crude product was stirred with TFA:DCM 1:1 for 1 hour, then evaporated and stirred with excess ethylenediamine in methanol until the deprotection was complete. The product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH), frozen and lyophilized to afford the free base (62 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (br s, 1H), 8.83 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 8.00 (d, J = 1.5 Hz, 1H), 7.87

(d, J = 1.6 Hz, 1H), 7.39 (d, J = 3.7 Hz, 1H), 6.81 (d, J = 3.6 Hz, 1H), 3.93 – 3.80 (m, 2H), 3.77 – 3.64 (m, 2H), 3.22 (s, 2H), 3.13 – 2.87 (m, 3H), 2.58 – 2.35 (m, 6H), 1.61 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -68.19 (s); LCMS $(M+H)^+$: 594.3.

Example 76. {trans-3-(4-{[4-(methoxymethyl)-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step A. [2-Chloro-6-(trifluoromethyl)pyridin-4-yl]methanol and [2-chloro-6-(trifluoromethyl)pyridin-3-yl]methanol

To a solution of 2-chloro-6-(trifluoromethyl)nicotinic acid (0.90 g, 4.0 mmol) and 2-chloro-6-(trifluoromethyl)isonicotinic acid (1.1 g, 4.9 mmol) (a mixture of regioisomers prepared in Example 75, Step A) in tetrahydrofuran (20 mL) cooled in an ice bath was added triethylamine (1.3 mL, 9.2 mmol) followed by isobutyl chloroformate (1.2 mL, 9.2 mmol, Aldrich). The reaction was stirred for 30 minutes, then was filtered through a short pad of celite into a flask containing sodium tetrahydroborate (1.0 g, 26 mmol) in water (10 mL) which was also cooled in an ice bath. Additional THF (10 mL) was used as a rinse through the celite into the reaction flask. After warming to room temperature, water was added and the layers separated. The THF layer was reserved and the aqueous was extracted with three portions of ethyl acetate which were combined with the original THF organic layer. The combined organic extracts were washed with brine,

dried over sodium sulfate, filtered and concentrated. Theoretical yield was assumed and the product used without further purificaiton, as a mixutre of regioisomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (dq, J = 7.8, 0.9 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.61 (s, 1H), 7.55 (s, 1H), 4.85 (s, 2H), 4.83 (s, 2H); LCMS $(M+H)^+$: 212.0.

Step B. 2-Chloro-4-(methoxymethyl)-6-(trifluoromethyl)pyridine(desired isomer isolated)

To a solution of [2-chloro-6-(trifluoromethyl)pyridin-4-yl]methanol (0.84 g, 4.0 mmol) and [2-chloro-6-(trifluoromethyl)pyridin-3-yl]methanol (0.84 g, 4.0 mmol) (as a mixture of regioisomers from Step A) in N,N-dimethylformamide (8.6 mL) was added potassium carbonate (3.3 g, 24 mmol), followed by methyl iodide (0.99 mL, 16 mmol). The reaction was stirred overnight. Additional DMF (10 mL), methyl iodide (2.0 mL, 32 mmol) and potassium carbonate (3.3 g, 24 mmol) were added and the reaction was stirred for72 hours. Water was added into the reaction and the product was extracted with three portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered and concentrated. Flash chromatography on silica gel, eluting with a gradient from 0-25% EtOAc/Hexanes allowed for isolation of desired isomer, contaminated with a small amount of the undesired isomer. Desired isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.50 (s, 1H), 4.53 (dd, 2H), 3.48 (s, 3H).

Step C. 4-(Methoxymethyl)-6-(trifluoromethyl)pyridine-2-carbonitrile

A solution of 2-chloro-4-(methoxymethyl)-6-(trifluoromethyl)pyridine (0.5 g, 2 mmol, from Step B) and zinc cyanide (1.56 g, 13.3 mmol) in N-methylpyrrolidinone (8 mL) was degassed by bubbling a stream of nitrogen through the solution for 10 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.51 g, 0.44 mmol) was added and the mixture was degassed similarly for 5 minutes. The reaction vial was sealed and heated in the microwave to 140 °C for 10 minutes. The reaction mixture was partitioned between water and ethyl acetate, and the aqueous portion was extracted with two further portions of ethyl acetate. The combined organic extracts were washed with water, followed by brine, dried over sodium sulfate, filtered and concentrated. Flash chromatography on silica gel, eluting with a gradient from 0-30% EtOAc/Hexanes afforded purified product

(0.36 g, 80%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.83 (m, 2H), 4.60 (dd, J = 0.9 Hz, 2H), 3.51 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.55 (s); LCMS $(M+H)^+$: 217.1.

Step D. 4-(Methoxymethyl)-6-(trifluoromethyl)pyridine-2-carboxylic acid

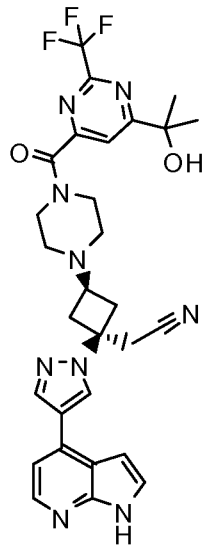
To a solution of 4-(methoxymethyl)-6-(trifluoromethyl)pyridine-2-carbonitrile (0.36 g, 1.7 mmol, from Step C) in ethanol (20 mL) was added 1.0 M sodium hydroxide in water (6.5 mL, 6.5 mmol) and the reaction was heated in an oil bath held at 90 °C for 4 hours. Upon cooling to room temperature, 1N HCl was added to achieve pH 2, and the product was extracted with ethyl acetate (3x). The combined extracts were dried over sodium sulfate, decanted and concentrated to afford a crystalline solid which was used without further purification. ^{1}H NMR (300 MHz, CD_3OD) δ 8.29 (s, 1H), 7.95 (s, 1H), 4.66 (s, 2H), 3.49 (s, 3H); ^{19}F NMR (282 MHz, CD_3OD) δ -69.56 (s); LCMS $(M+H)^+$: 236.0.

Step E. {trans-3-(4-{[4-(Methoxymethyl)-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

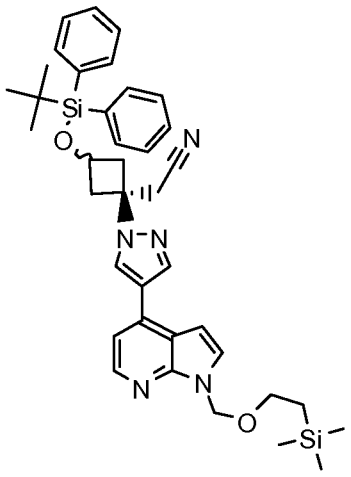
4-(Methoxymethyl)-6-(trifluoromethyl)pyridine-2-carboxylic acid (0.0470 g, 0.200 mmol, from Step D) was dissolved in N,N-dimethylformamide (5 mL) and to this was added {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.100 g, 0.203 mmol, from Step 1 of Example 1b), followed by benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (106.1 mg, 0.2398 mmol) and triethylamine (0.14 mL, 1.0 mmol). After stirring overnight, the reaction mixture was partitioned between ethyl acetate and brine. The aqueous portion was extracted a further two times with ethyl acetate. The combined extracts were dried over sodium sulfate, filtered and concentrated. The crude product was stirred with TFA:DCM 1:1 for 1 hour, evaporated, then stirred with excess ethylenediamine in methanol until the deprotection was complete. The product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH), frozen and lyophilized

to afford the free base (49 mg, 42%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.14 (br s, 1H), 8.85 (s, 1H), 8.48 (s, 1H), 8.34 (s, 1H), 7.84 (s, 1H), 7.74 (d, *J* = 1.4 Hz, 1H), 7.41 (d, *J* = 3.7 Hz, 1H), 6.81 (d, *J* = 3.6 Hz, 1H), 4.57 (s, 2H), 3.94 – 3.80 (m, 2H), 3.76 – 3.61 (m, 2H), 3.48 (s, 3H), 3.22 (s, 2H), 3.12 – 2.80 (m, 3H), 2.60 – 2.34 (m, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -68.34 (s); LCMS $(M+H)^+$: 580.3.

Example 77. {cis-3-(4-{[6-(1-hydroxy-1-methylethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



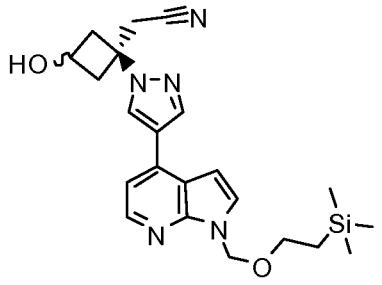
Step A. {3-{[tert-Butyl(diphenyl)silyl]oxy}-1-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (a mixture of diastereomers)



To a solution of (3-{[tert-butyl(diphenyl)silyl]oxy}cyclobutylidene)acetonitrile (4.0 g, 8.7 mmol, from Step 4 of Example 1a) and 4-(1H-pyrazol-4-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridine (1.50 g, 4.77 mmol, US 20090181959) in acetonitrile (10 mL, 200 mmol) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.68 mL, 4.6 mmol). The reaction was stirred overnight. A further portion of 1,8-diazabicyclo[5.4.0]undec-7-ene (0.7 mL, 5 mmol) was added and the reaction was allowed to continue for an additional 72 hours. Acetonitrile was removed *in vacuo*. Flash chromatography on silica gel, eluting with 0% - 30% EtOAc/Hexanes, was used to purify product, which was obtained as a mixture of diastereomers (2 g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 5.0 Hz, 1H major), 8.29 (d, J = 5.0 Hz, 1H minor), 8.06 (s, 1H major), 8.03 (s, 1H major), 8.00 (s, 1H minor), 7.93 (s, 1H minor), 7.70 – 7.31 (m, 10H major and 10H minor), 7.19 (d, J = 5.0 Hz, 1H major), 7.11 (d, J = 5.0 Hz, 1H minor), 6.74 (d, J = 3.6 Hz, 1H major), 6.63 (d, J = 3.7 Hz, 1H minor), 5.71 (s, 2H major), 5.69 (s, 2H minor), 4.49-4.39 (m, 1H minor), 4.33 (tt, J = 7.0, 7.0 Hz, 1H major), 3.67 – 3.45 (m, 2H major and 2H minor), 3.22 (s, 2H minor), 3.11 – 2.95 (m, 2H minor), 2.92 – 2.77 (m, 6H major), 2.65 – 2.50 (m, 2H minor), 1.08 (s, 9H minor), 1.03 (s, 9H major), 0.98 – 0.80 (m, 2H major and 2H minor), -0.06 (s, 9H major), -0.08 (s, 9H minor); LCMS $(M+H)^+$: 662.1.

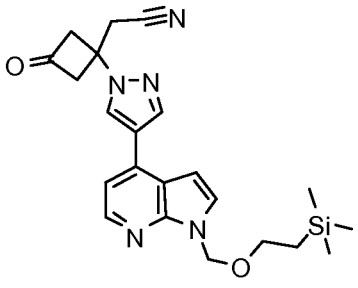
Step B. {3-hydroxy-1-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-

4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile(a mixture of diastereomers)



To {3-{[tert-butyl(diphenyl)silyl]oxy}-1-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (2.0 g, 3.0 mmol, a mixture of diastereomers from Step A) ethanol (82 mL) was added 5.0 M sodium hydroxide in water (9 mL, 50 mmol). The reaction was stirred overnight. The reaction mixture was diluted with water and ethanol was removed *in vacuo*. The aqueous mixture was extracted with ethyl acetate (3x). The combined organic extracts were washed with water, then brine, dried over sodium sulfate, decanted and concentrated. The product, as a mixture of diastereomers, was used without further purification in Step C. LCMS $(M+H)^+$: 424.2.

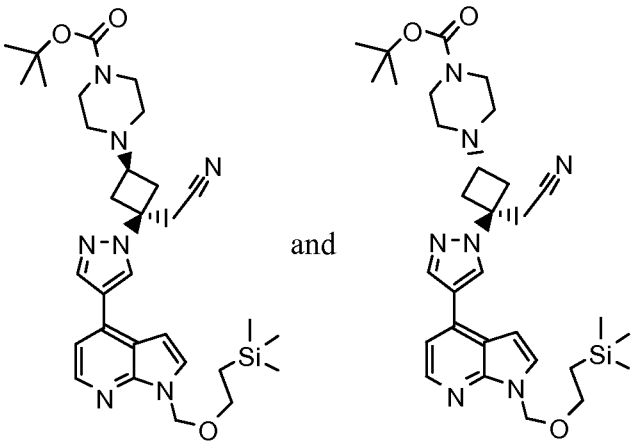
Step C. {3-oxo-1-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



To a solution of {3-hydroxy-1-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (1.3 g, 3.1 mmol, a

mixture of diastereomers from Step B) in methylene chloride (40 mL) was added Dess-Martin periodinane (1.63 g, 3.84 mmol). After stirring for 1 hour and 15 minutes, the reaction mixture was poured into 1N NaOH and extracted with three portions of DCM. The combined extracts were washed with 1N NaOH, then brine, dried over sodium sulfate, decanted and solvent was removed *in vacuo*. Flash chromatography on silica gel, eluting with an initial gradient from 0-30% EtOAc/Hexanes, then a rapid gradient up to 100% EtOAc afforded product (1.1 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, J = 5.0 Hz, 1H), 8.14 (s, 1H), 8.11 (s, 1H), 7.42 (d, J = 3.7 Hz, 1H), 7.18 (d, J = 5.0 Hz, 1H), 6.71 (d, J = 3.7 Hz, 1H), 5.71 (s, 2H), 4.10 – 3.97 (m, 2H), 3.74 – 3.61 (m, 2H), 3.61 – 3.47 (m, 2H), 3.28 (s, 2H), 0.98 – 0.86 (m, 2H), -0.07 (s, 9H); LCMS $(M+H)^+$: 422.2.

Step D. tert-butyl 4-{cis-3-(cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazine-1-carboxylate and tert-butyl 4-{trans-3-(cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazine-1-carboxylate (each diastereomer isolated)

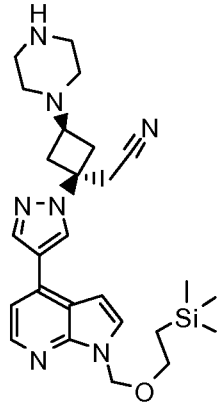


Zinc dichloride (0.210 g, 1.54 mmol) and sodium cyanoborohydride (0.194 g, 3.08 mmol) were combined in methanol (6.5 mL) (according to the procedure found in JOC 1985, 50, 1927-1932) and stirred for 2 hours. After the reducing mixture was generated, {3-oxo-1-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (1.10 g, 2.61 mmol, from Step C) and tert-

butyl piperazine-1-carboxylate (1.15 g, 6.17 mmol, Aldrich) were combined in methanol (30 mL) to dissolve, then the reducing solution generated by the combination of Zinc dichloride and sodium cyanoborohydride was added. The reaction was stirred overnight. Methanol was removed *in vacuo*. Saturated sodium bicarbonate solution was added and the solution was extracted with three portions of ethyl acetate. The combined extracts were dried over sodium sulfate, filtered and concentrated. Flash chromatograpy on silica gel, eluting with a gradient from 0-10% MeOH in DCM afforded product (1.27 g, 82%) as a mixture of diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, J = 5.1 Hz, 1H), 8.31 (d, J = 5.0 Hz, 1H), 8.12 (s, 1H), 8.08 (s, 1H), 8.04 (s, 1H), 8.04 (s, 1H), 7.41 (d, J = 3.7 Hz, 1H), 7.40 (d, J = 3.7 Hz, 1H), 7.19 (d, J = 5.1 Hz, 1H), 7.17 (d, J = 5.8 Hz, 1H), 6.73 (d, J = 3.1 Hz, 1H), 6.71 (d, 1H), 5.71 (s, 4H), 3.59 – 3.50 (m, 4H), 3.45 (m, 8H), 3.19 (s, 2H), 3.11 (s, 2H), 3.07 – 2.95 (m, 2H), 2.94 – 2.60 (m, 6H), 2.53 – 2.39 (m, 2H), 2.33 (m, 8H), 1.61 (s, 18H), 0.99 – 0.73 (m, 4H), -0.07 (d, J = 0.7 Hz, 18H).

Chiral HPLC was used to separate the cis and trans isomers : CHIRALPAK IA column, 30% EtOH/Hexanes at 14 mL/min, ~75 mg/injection, Peak 1 retention time: 9.725 min; Peak 2 retention time: 12.804 min.

Step E. {cis-3-Piperazin-1-yl-1-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



tert-Butyl 4-{cis-3-(cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazine-1-carboxylate (0.7 g, 1 mmol, peak 1 from Step D) was dissolved in 1,4-dioxane (14 mL) and 4.0 M hydrogen

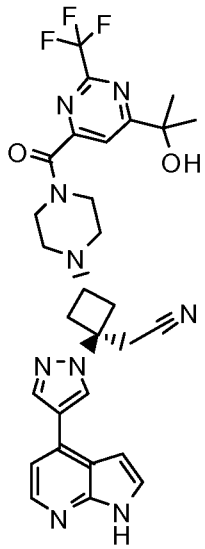
chloride in dioxane (10 mL, 40 mmol) was added. After stirring for 72 hours, water (10 mL) was added and the heterogeneous mixture became a solution, and the reaction then proceeded. After stirring for 5 hours, the reaction mixture was poured into saturated sodium bicarbonate solution to neutralize and dioxane was removed *in vacuo*. The aqueous mixture was extracted with ethyl acetate (4x) and the combined extracts were dried over sodium sulfate, filtered and concentrated. (0.56 g, 93%). LCMS $(M+H)^+$: 492.1.

Step F. {cis-3-(4-{[6-(1-Hydroxy-1-methylethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

6-(1-Hydroxy-1-methylethyl)-2-(trifluoromethyl)pyrimidine-4-carboxylic acid (0.0125 g, 0.0501 mmol, Example 58, Step B) was dissolved in N,N-dimethylformamide (1 mL), and to this was added {cis-3-piperazin-1-yl-1-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.025 g, 0.051 mmol, from Step E, stemming from Peak 1 of Step D), followed by benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (26.57 mg, 0.06008 mmol) and triethylamine (0.035 mL, 0.25 mmol). After stirring overnight, the reaction mixture was partitioned between ethyl acetate and brine, and the aqueous portion was extracted with ethyl acetate a further two times. The combined extracts were dried over sodium sulfate, filtered and concentrated. The crude product was stirred with TFA:DCM 1:1 for 1 hour, evaporated, then stirred with ethylenediamine (1.5 mL) in methanol (5 mL) overnight. The product was purified via preparative HPLC-MS (C18 eluting with a gradient of $MeCN/H_2O$ containing 0.15% NH_4OH), frozen and lyophilized to afford the free base (5 mg, 20%).^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.30 (d, J = 5.0 Hz, 1H), 8.06 (s, 1H), 8.05 (s, 2H), 7.37 (d, J = 3.5 Hz, 1H), 7.18 (d, J = 5.1 Hz, 1H), 6.72 (d, J = 3.6 Hz, 1H), 3.90 – 3.78 (m, 2H), 3.69 – 3.58 (m, 2H), 3.12 (s, 2H), 2.94 (tt, J = 7.2, 7.7 Hz, 1H), 2.88 – 2.78 (m, 2H), 2.78 – 2.63 (m, 2H), 2.57 – 2.50 (m, 2H), 2.50 – 2.41 (m, 2H), 1.62 (s, 6H).

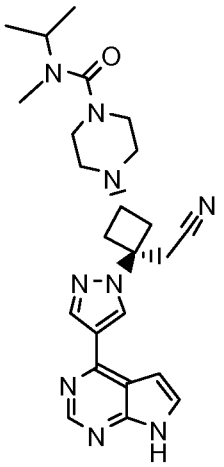
^{19}F NMR (282 MHz, $cdcl_3$) δ -70.71 (s); LCMS $(M+H)^+$: 594.1.

Example 78. {trans-3-(4-{[6-(1-hydroxy-1-methylethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



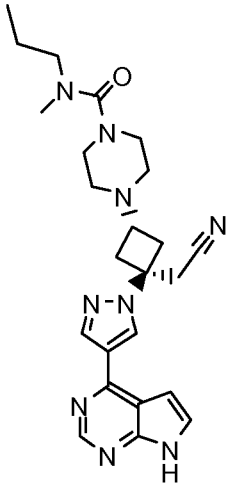
The title compound was prepared in the manner of Example 77, starting with Peak 2 from Step D to afford product as the free base (5 mg, 20%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.31 (d, *J* = 5.0 Hz, 1H), 8.14 (s, 1H), 8.10 (s, 1H), 8.08 (s, 1H), 7.40 (d, *J* = 3.5 Hz, 1H), 7.19 (d, *J* = 5.0 Hz, 1H), 6.72 (d, *J* = 3.5 Hz, 1H), 3.97 – 3.83 (m, 2H), 3.76 – 3.51 (m, 2H), 3.19 (s, 2H), 3.11 – 3.00 (m, 2H), 2.98 (tt, *J* = 6.5, 6.8 Hz, 1H), 2.59 – 2.39 (m, 6H), 1.62 (s, 6H); ^{19}F NMR (282 MHz, $cdcl_3$) δ -70.71 (s); LCMS $(M+H)^+$: 594.1.

Example 79. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-isopropyl-N-methylpiperazine-1-carboxamide



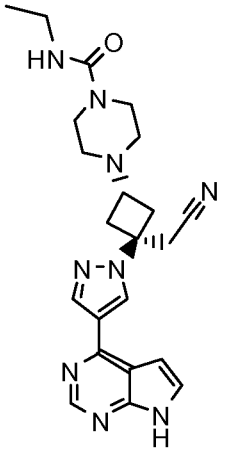
To N-methyl-2-propanamine (13.4 μL, 0.183 mmol, Aldrich), in acetonitrile (0.5 mL) was added 1.89 M phosgene in toluene (0.193 mL, 0.365 mmol) followed by N,N-diisopropylethylamine (0.0318 mL, 0.183 mmol). After stirring for 1 hour, solvents and excess reagents were removed *in vacuo*. The residue was reconstituted in 1:1 MeCN:DCM and N,N-diisopropylethylamine (0.0318 mL, 0.183 mmol) was added, followed by{trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, from Step 1 of Example 1b) and the reaction mixture was stirred overnight. The mixture was diluted with water, and extracted with EtOAc. The extract was washed with water, brine, dried over sodium sulfate and concentrated. The residue was stirred with 1:1 TFA:DCM for 1 hour, evaporated, then stirred with 0.2 mL ethylenediamine in methanol. The product was purified by preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH), frozen and lyophilized to afford product as the free base (12.8 mg, 46%). ^{1}H NMR (400 MHz, dmso) δ 12.06 (br s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, 1H), 7.07 (d, 1H), 3.90 (hept, 1H), 3.42 (s, 2H), 3.14 – 3.04 (m, 4H), 3.04 – 2.94 (m, 2H), 2.79 (tt, J = 7.2, 7.3 Hz, 1H), 2.60 (s, 3H), 2.42 – 2.21 (m, 6H), 1.04 (d, 6H); LCMS $(M+H)^+$: 462.3.

Example 80. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-methyl-N-propylpiperazine-1-carboxamide



The title compound was prepared according to the procedure of Example 79, using N-methyl-n-propylamine (18.7 μL, 0.183 mmol, Acros) to afford product as the free base (13 mg, 46%). ^{1}H NMR (400 MHz, dmso) δ 12.10 (br s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, 1H), 7.07 (d, 1H), 3.42 (s, 2H), 3.10 (m, 4H), 3.06 – 2.92 (m, 4H), 2.78 (tt, *J* = 7.5, 7.8 Hz, 1H), 2.72 (s, 3H), 2.40 – 2.18 (m, 6H), 1.54 – 1.38 (m, 2H), 0.79 (t, 3H); LCMS (M+H)$^+$: 462.3.

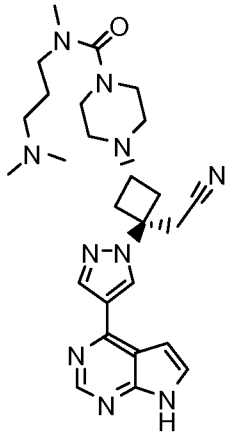
Example 81. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-ethylpiperazine-1-carboxamide



{trans-3-Piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (30.0 mg, 0.0609

mmol, from Step 1 of Example 1b) was dissolved in acetonitrile (0.40 mL) and ethane, isocyanato- (8.6 mg, 0.12 mmol, Aldrich) was added. After stirring for 1 hour, solvent and excess reagent was removed *in vacuo*. The residue was stirred with 1:1 TFA:DCM for 1 hour, evaporated, then stirred with 0.2 mL ethylenediamine in methanol until deprotection was complete. The product was purified by preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH), frozen and lyophilized to afford product as the free base (16.7 mg, 63%). ^{1}H NMR (400 MHz, dmso) δ 12.06 (br s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, 1H), 7.07 (d, 1H), 6.47 (t, 1H), 3.42 (s, 2H), 3.32 – 3.21 (m, 4H), 3.08 – 2.93 (m, 4H), 2.76 (tt, J = 7.3, 7.3 Hz, 1H), 2.40 – 2.30 (m, 2H), 2.28 – 2.15 (m, 4H), 0.99 (t, J = 7.1 Hz, 3H); LCMS $(M+H)^+$: 434.1.

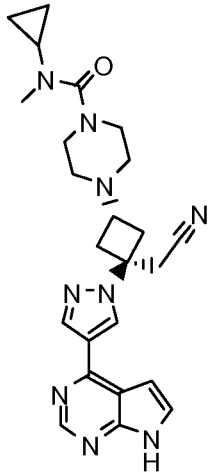
Example 82. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[3-(dimethylamino)propyl]-N-methylpiperazine-1-carboxamide



To N,N,N'-trimethylpropane-1,3-diamine (0.0212 g, 0.183 mmol, Alfa Aesar) in acetonitrile (0.5 mL) was added 1.89 M phosgene in toluene (0.193 mL, 0.365 mmol) . After stirring for 1 hour, solvent was removed *in vacuo*. The residue was dissolved in 1:1 MeCN:DCM and {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, from Step 1 of Example 1b) and N,N-diisopropylethylamine (64 μL, 0.36 mmol) were added and the mixture was stirred overnight. The mixture was diluted with water and was extracted with EtOAc. The extract was washed with water, brine, dried over

sodium sulfate and concentrated. The residue was stirred with 1:1 TFA:DCM for 1 hour, evaporated, then stirred with 0.2 mL ethylenediamine in methanol until deprotection was complete. The product was purified by preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH), frozen and lyophilized to afford product as the free base (10.3 mg, 34%). ^{1}H NMR (400 MHz, dmso) δ 12.10 (s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, J = 3.5 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 3.42 (s, 2H), 3.14 – 2.93 (m, 8H), 2.77 (tt, J = 7.4, 7.5 Hz, 1H), 2.73 (s, 3H), 2.40 – 2.23 (m, 6H), 2.13 (t, J = 7.0 Hz, 2H), 2.09 (s, 6H), 1.58 (p, J = 7.0 Hz, 2H); LCMS $(M+H)^+$: 505.2.

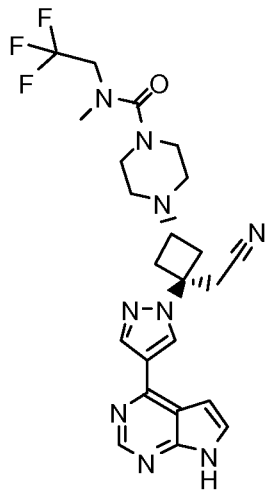
Example 83. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-cyclopropyl-N-methylpiperazine-1-carboxamide



The title compound was prepared by the method of Example 79, using N-methylcyclopropanamine hydrochloride (0.0196 g, 0.183 mmol, Accela ChemBio, Inc.) to afford product as the free base (21.8 mg, 78%). ^{1}H NMR (400 MHz, dmso) δ 11.98 (br s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 3.42 (s, 2H), 3.26 – 3.17 (m, 4H), 3.04 – 2.94 (m, 2H), 2.78 (tt, J = 7.3, 7.4 Hz, 1H), 2.70 (s, 3H), 2.57 (tt, J = 6.9, 3.7 Hz, 1H), 2.39 – 2.31 (m, 2H), 2.31 – 2.22 (m, 4H), 0.63 (td, J = 6.9, 4.9 Hz, 2H), 0.50 – 0.44 (m, 2H); LCMS $(M+H)^+$: 460.3.

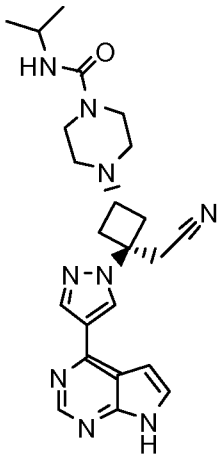
Example 84. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-

pyrazol-1-yl]cyclobutyl}-N-methyl-N-(2,2,2-trifluoroethyl)piperazine-1-carboxamide



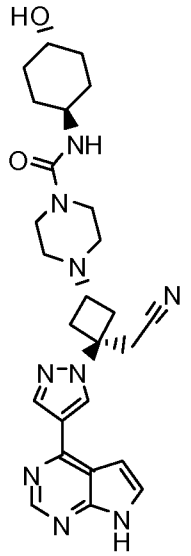
The title compound was prepared by the method of Example 79, using 2,2,2-trifluoro-N-methylethanamine hydrochloride (0.0273 g, 0.183 mmol, Matrix Scientific) to afford product as the free base (11.5 mg, 38%). ^{1}H NMR (376 MHz, dmso) δ 12.11 (br s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 4.04 (q, J = 9.8 Hz, 2H), 3.42 (s, 2H), 3.24 – 3.11 (m, 4H), 3.04 – 2.96 (m, 2H), 2.94 (s, 3H), 2.79 (tt, J = 7.3, 7.3 Hz, 1H), 2.40 – 2.26 (m, 6H); ^{19}F NMR (376 MHz, dmso) δ -70.04 (t, J = 9.7 Hz); LCMS $(M+H)^+$: 502.2.

Example 85. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-isopropylpiperazine-1-carboxamide



To a solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, from Step 1 of Example 1b) in methylene chloride (1 mL) was added N,N-diisopropylethylamine (26 μL, 0.15 mmol) followed by 2-isocyanatopropane (7 μL, 0.07 mmol, Aldrich) and the reaction was stirred for two hours. TFA (1 mL) was added and the reaction was stirred for 1 hour, then evaporated. The residue was redissolved in methanol (1.8 mL) and ethylenediamine (0.2 mL) was added. After stirring for 30 minutes, the product was purified by preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH), the eluent was frozen and lyophilized to afford product as the free base (9 mg, 30%). ^1H NMR (300 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.39 (s, 1H), 7.50 (d, J = 3.7 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 3.94 – 3.78 (m, 1H), 3.49 – 3.37 (m, 4H), 3.33 (s, 2H), 3.14 – 3.00 (m, 2H), 2.97 – 2.85 (m, 1H), 2.57 – 2.43 (m, 2H), 2.43 – 2.31 (m, 4H), 1.12 (d, J = 6.7 Hz, 6H); LCMS $(M+H)^+$: 448.1.

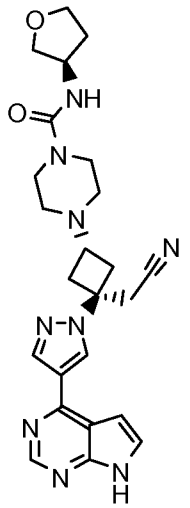
Example 86. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-(trans-4-hydroxycyclohexyl)piperazine-1-carboxamide



To a vial containing Phoxime® resin (0.19 g, Aldrich) was added trans-4-aminocyclohexanol (56 mg, 0.49 mmol, Aldrich) in methylene chloride (2.5 mL). The reaction was stirred overnight. The resin was collected by filtration and washed with

DCM, then with MeOH. The collected resin was returned to a reaction vial and swelled with 1,2-Dichloroethane (2 mL). {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.040 g, 0.081 mmol, from Step 1 of Example 1b) as a solution in methylene chloride (1 mL) was added, followed by Toluene (5 mL). The vials was sealed and heated to 80 °C overnight. After cooling to room temperature, the resin was removed by filtration and washed with DCM and MeOH, and the filtrate was evaporated. The residue was stirred with 1:1 TFA:DCM for 1 hour, evaporated, then stirred with ethylenediamine (0.2 mL) in methanol (1.5 mL) until the deprotection was complete. The product was purified by preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH), the eluent was frozen and lyophilized to afford product as the free base (5 mg, 10%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.39 (s, 1H), 7.51 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 3.56 – 3.44 (m, 2H), 3.44 – 3.37 (m, 4H), 3.33 (s, 2H), 3.13 – 3.02 (m, 2H), 2.95 – 2.83 (m, 1H), 2.55 – 2.44 (m, 2H), 2.41 – 2.33 (m, 4H), 1.98 – 1.80 (m, 4H), 1.40 – 1.20 (m, 4H); LCMS $(M+H)^+$: 504.4.

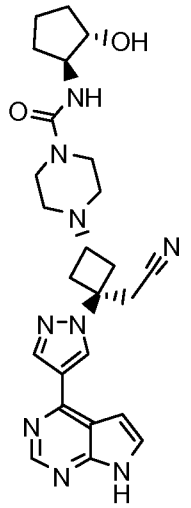
Example 87. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(3R)-tetrahydrofuran-3-yl]piperazine-1-carboxamide



The title compound was prepared according to the method of Example 86, starting

with (3R)-tetrahydrofuran-3-amine 4-methylbenzenesulfonate (0.13 g, 0.49 mmol, Fluka), which was stirred with triethylamine (0.068 mL, 0.49 mmol) in DCM (2.5 mL) before adding the resulting mixture to the Phoxime® resin. Purified to afford product as the free base (5 mg, 10%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.39 (s, 1H), 7.51 (d, J = 3.7 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 4.34 – 4.17 (m, 1H), 3.98 – 3.81 (m, 2H), 3.76 (td, J = 8.3, 6.1 Hz, 1H), 3.56 (dd, J = 9.1, 4.3 Hz, 1H), 3.50 – 3.38 (m, 4H), 3.33 (s, 2H), 3.14 – 2.95 (m, 2H), 2.98 – 2.83 (m, 1H), 2.56 – 2.43 (m, 2H), 2.44 – 2.32 (m, 4H), 2.18 (dq, J = 14.8, 7.4 Hz, 1H), 1.92 – 1.72 (m, 1H); LCMS $(M+H)^+$: 476.2.

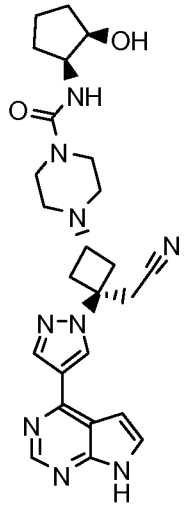
Example 88. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-(2-hydroxycyclopentyl)piperazine-1-carboxamide (racemic)



The title compound was prepared by the method of Example 87 using a mixture of trans-2-aminocyclopentanol hydrochloride (67 mg, 0.49 mmol, racemic) and triethylamine (0.068 mL, 0.49 mmol) in methylene chloride (2.5 mL). The racemic product was obtained as the free base (5 mg, 10%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.62 (s, 1H), 8.57 (s, 1H), 8.31 (s, 1H), 7.42 (d, J = 3.6 Hz, 1H), 6.89 (d, J = 3.7 Hz, 1H), 3.83 (q, J = 6.2 Hz, 1H), 3.74 – 3.63 (m, 1H), 3.39 – 3.30 (m, 4H), 3.23 (s, 2H), 3.04 – 2.90 (m, 2H), 2.86 – 2.71 (m, 1H), 2.45 – 2.36 (m, 2H), 2.36 – 2.25 (m, 4H), 2.05 – 1.89 (m, 1H), 1.89 – 1.77 (m, 1H), 1.67 – 1.51 (m, 2H), 1.51 – 1.25 (m, 2H); LCMS $(M+H)^+$:

490.4.

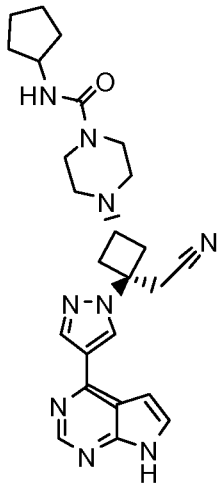
Example 89. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1S,2R)-2-hydroxycyclopentyl]piperazine-1-carboxamide (single enantiomer produced)



To a solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, from Step 1 of Example 1b) in acetonitrile (1 mL) was added 1.89 M phosgene in toluene (0.042 mL, 0.079 mmol) followed by N,N-diisopropylethylamine (0.021 mL, 0.12 mmol). After stirring for 1 hour, solvent and excess reagents were removed *in vacuo*. The residue was redissolved in methylene chloride (0.2 mL) and (1R,2S)-2-aminocyclopentanol hydrochloride (0.025 g, 0.18 mmol, Fluka) followed by N,N-diisopropylethylamine (0.04 mL, 0.2 mmol) were added. After 45 minutes, additional (1R.2S)-2-aminocyclopentanol hydrochloride (0.025 g, 0.18 mmol) and N,N-diisopropylethylamine (0.04 mL, 0.2 mmol) were added. TFA (0.2 mL) was added, the reaction was stirred for 3 hours, and then the solvent was removed. Deprotection was completed by stirring with excess ethylenediamine in methanol and the product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) to afford the free base (13 mg, 44%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.51 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 3.7 Hz, 1H), 4.07 (td, J = 4.5, 2.0 Hz, 1H), 3.86 (ddd, J = 9.9, 7.6,

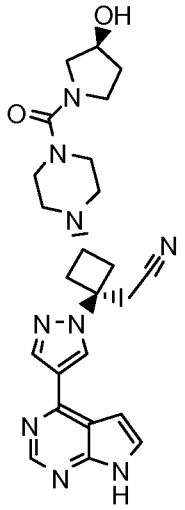
4.4 Hz, 1H), 3.49 – 3.42 (m, 4H), 3.34 (s, 2H), 3.11 – 3.03 (m, 2H), 2.91 (tt, *J* = 6.7, 6.8 Hz, 1H), 2.55 – 2.45 (m, 2H), 2.44 – 2.36 (m, 4H), 1.96 – 1.71 (m, 3H), 1.71 – 1.48 (m, 3H); LCMS $(M+H)^+$: 490.1.

Example 90. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-cyclopentylpiperazine-1-carboxamide



The title compound was prepared by the method of Example 85, using isocyanatocyclopentane (8.2 uL, 0.073 mmol, Aldrich) and omitting DIPEA, to afford the product as the free base (13 mg, 45%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.39 (s, 1H), 7.51 (d, *J* = 3.6 Hz, 1H), 6.98 (d, *J* = 3.7 Hz, 1H), 4.07 – 3.86 (m, 2H), 3.48 – 3.37 (m, 4H), 3.32 (s, 2H), 3.13 – 2.99 (m, 2H), 2.91 (tt, *J* = 7.3, 7.6 Hz, 1H), 2.56 – 2.43 (m, 2H), 2.44 – 2.29 (m, 4H), 1.99 – 1.76 (m, 2H), 1.80 – 1.62 (m, 2H), 1.62 – 1.47 (m, 2H), 1.48 – 1.27 (m, 2H); LCMS $(M+H)^+$: 474.1.

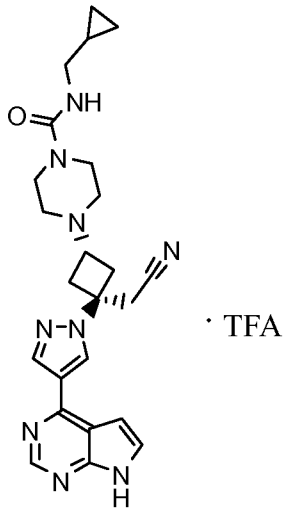
Example 91. {trans-3-(4-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



(3S)-Pyrrolidin-3-ol (0.011 g, 0.12 mmol, Aldrich) was dissolved in methylene chloride (0.2 mL) and acetonitrile (1 mL) and 1.89 M phosgene in toluene (0.097 mL, 0.18 mmol) and N,N-diisopropylethylamine (0.021 mL, 0.12 mmol) were added. The reaction mixture was stirred at room temperature for 1 hour, followed by evaporation of solvent and excess reagent. N,N-Diisopropylethylamine (0.062 mL, 0.35 mmol) was again added followed by acetonitrile (0.5 mL), and a solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, from Step 1 of Example 1b) in methylene chloride (1 mL) was added. The reaction was stirred overnight. TFA (1 mL) was added and the reaction was stirred for 1 hour. Solvents were evaporated and replaced with methanol (1.8 mL) and ethylenediamine (0.2 mL). After stirring for 30 minutes, the product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) to afford the free base (3 mg, 10%). ^1H NMR (400 MHz, CD_3OD) δ 8.72 (s, 1H), 8.67 (s, 1H), 8.40 (s, 1H), 7.51 (d, J = 3.6 Hz, 1H), 6.99 (d, J = 3.6 Hz, 1H), 4.41 – 4.29 (m, 1H), 3.70 – 3.50 (m, 2H), 3.45 – 3.15 (m, 8H), 3.14 – 3.00 (m, 2H), 2.93 (tt, J = 7.0, 7.0 Hz, 1H), 2.56 – 2.32 (m, 6H), 2.04 – 1.68 (m, 2H); LCMS $(M+H)^+$: 476.1.

Example 92. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-(cyclopropylmethyl)piperazine-1-carboxamide

trifluoroacetate salt

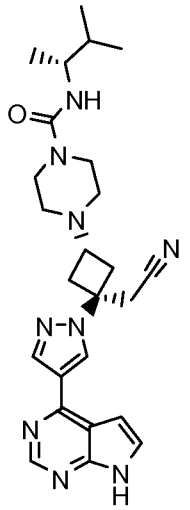


· TFA

To a solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.021 g, 0.043 mmol, from Step 1 of Example 1b) in acetonitrile (1 mL) was added 1.89 M phosgene in toluene (0.042 mL, 0.079 mmol) followed by N,N-diisopropylethylamine (0.021 mL, 0.12 mmol). After stirring for 1 hour, excess reagents and solvent were removed *in vacuo*. The product was reeconstituted in methylene chloride (0.2 mL) and 1-cyclopropylmethanamine hydrochloride (80 mg, 0.74 mmol, Aldrich) followed by N,N-diisopropylethylamine (0.080 mL, 0.46 mmol) were added. The reaction was stirred overnight and then evaporated under a stream of nitrogen. The residue was reconstituted in DCM and TFA was added (1:1). After 1 hour, these solvents were evaporated and replaced with ethylenediamine (0.2 mL) in methanol. When deprotection was complete, the product was purified via two successive preparative HPLC-MS runs (first: C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH; followed by C18 eluting with a gradient of MeCN/H_2O containing 0.1% TFA) to afford the product as the trifluoroacetate salt (6 mg). ^{1}H NMR (400 MHz, CD_3OD) δ 9.02 (s, 1H), 8.87 (s, 1H), 8.53 (s, 1H), 7.80 (d, J = 3.7 Hz, 1H), 7.27 (d, J = 3.7 Hz, 1H), 3.93 (tt, J = 8.8, 9.1 Hz, 1H), 3.73 (br m, 4H), 3.51 – 3.36 (m, 4H), 3.21 (br m, 4H), 3.07 – 2.90 (m, 4H), 0.98 (dddd, J = 14.9, 8.1, 7.2, 3.7 Hz, 1H), 0.45 (ddd, 2H), 0.18 (dt, J = 6.0, 4.5 Hz, 2H);

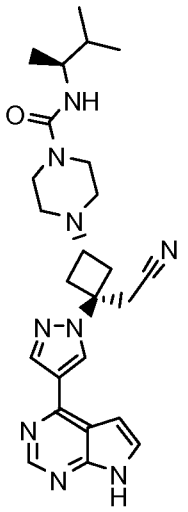
LCMS $(M+H)^+$: 460.2.

Example 93. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1R)-1,2-dimethylpropyl]piperazine-1-carboxamide



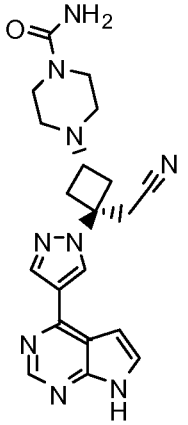
The title compound was prepared by the method of Example 92, using (2R)-3-methylbutan-2-amine (0.05 g, 0.6 mmol, Aldrich) and purified by preparative HPLC-MS (C18 eluting with a gradient of $MeCN/H_2O$ containing 0.15% NH_4OH) to afford product as the free base (7 mg, 30%). ^1H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.39 (s, 1H), 7.50 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 3.64 – 3.52 (m, 1H), 3.51 – 3.38 (m, 4H), 3.33 (s, 2H), 3.13 – 2.98 (m, 2H), 2.91 (tt, J = 7.3, 7.5 Hz, 1H), 2.54 – 2.46 (m, 2H), 2.45 – 2.34 (m, 4H), 1.66 (h, J = 6.8 Hz, 1H), 1.07 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); LCMS $(M+H)^+$: 476.3.

Example 94. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1S)-1,2-dimethylpropyl]piperazine-1-carboxamide



The title compound was prepared by the method of Example 92, using (2S)-3-methylbutan-2-amine (0.05 g, 0.6 mmol, Alfa Aesar) and purified by preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) to afford product as the free base (7 mg, 30%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.51 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 3.58 (tt, 1H), 3.51 – 3.38 (m, 4H), 3.33 (s, 2H), 3.12 – 3.00 (m, 2H), 2.91 (tt, J = 7.2, 7.2 Hz, 1H), 2.54 – 2.45 (m, 2H), 2.44 – 2.31 (m, 4H), 1.67 (dq, J = 13.4, 6.6 Hz, 1H), 1.07 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); LCMS $(M+H)^+$: 476.4.

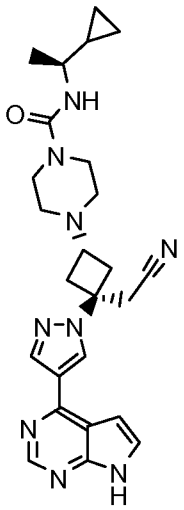
Example 95. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazine-1-carboxamide



The title compound was obtained as a by-product when following the procedure

of Example 92 using (1R)-1-cyclopropylethanamine (0.05 mL, 0.5 mmol, Alfa Aesar). The cyclopropylethyl substituent was unstable to the TFA step of the deprotection. The byproduct was isolated in pure form via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) (7 mg, 40%). ^1H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.39 (s, 1H), 7.50 (d, J = 3.7 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 3.52 – 3.42 (m, 4H), 3.33 (s, 2H), 3.11 – 2.96 (m, 2H), 2.91 (tt, J = 7.0, 7.1 Hz, 1H), 2.56 – 2.44 (m, 2H), 2.44 – 2.33 (m, 4H); LCMS $(M+H)^+$: 406.1.

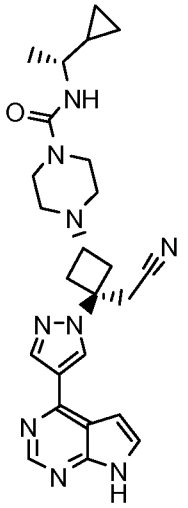
Example 96. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1S)-1-cyclopropylethyl]piperazine-1-carboxamide



To a solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.100 g, 0.203 mmol, from Step 1 of Example 1b) in DCM (1 mL) was added TFA (1 mL). After stirring for 1 hour, solvents were removed *in vacuo*. The residue was dissolved in MeOH (1.5 mL) and ethylenediamine (0.5 mL) was added and stirring continued until deprotection was determined to be complete by LCMS. Purification via preparative HPLC-MS (C18, eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) afforded product as the free base (0.030 g, 41%; M+H=363.2). To a solution of {trans-3-piperazin-1-yl-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.015 g, 0.041 mmol) in acetonitrile (2

mL) and methylene chloride (2 mL), was added 1.89 M phosgene in toluene (0.022 mL, 0.041 mmol) followed by N,N-diisopropylethylamine (0.0072 mL, 0.041 mmol). After stirring for 15 minutes, (1S)-1-cyclopropylethanamine (0.023 mL, 0.24 mmol, Alfa Aesar) was added. The product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) to afford the free base (8 mg, 40%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.51 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 3.7 Hz, 1H), 3.48 – 3.39 (m, 4H), 3.33 (s, 2H), 3.21 – 3.10 (m, 1H), 3.11 – 3.02 (m, 2H), 2.92 (tt, J = 7.1, 7.4 Hz, 1H), 2.54 – 2.45 (m, 2H), 2.44 – 2.34 (m, 4H), 1.19 (d, J = 6.7 Hz, 3H), 0.88 (tdd, J = 8.3, 4.9, 3.4 Hz, 1H), 0.51 – 0.43 (m, 1H), 0.43 – 0.35 (m, 1H), 0.28 (ddd, J = 9.8, 4.9 Hz, 1H), 0.15 (ddd, J = 9.3, 4.8 Hz, 1H); LCMS $(M+H)^+$: 474.2.

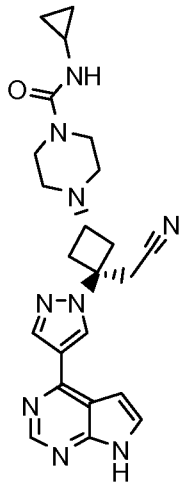
Example 97. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1R)-1-cyclopropylethyl]piperazine-1-carboxamide



The procedure of Example 96 was followed, using {trans-3-piperazin-1-yl-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.010 g, 0.027 mmol, prepared as described in that Example) and (1R)-1-cyclopropylethanamine (0.010 mL, 0.11 mmol, Alfa Aesar). The product was obtained as the free base (5 mg, 40%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.51 (d, J = 3.8 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 3.48 – 3.39 (m, 4H), 3.33 (s, 2H), 3.21 – 3.01 (m,

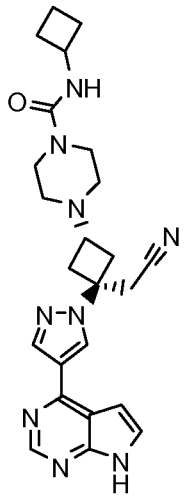
3H), 2.99 – 2.81 (m, 1H), 2.59 – 2.45 (m, 2H), 2.45 – 2.32 (m, 4H), 1.19 (d, J = 6.7 Hz, 3H), 1.03 – 0.65 (m, 1H), 0.59 – 0.33 (m, 2H), 0.34 – 0.22 (m, 1H), 0.22 – 0.09 (m, 1H); LCMS $(M+H)^+$: 474.2.

Example 98. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-cyclopropylpiperazine-1-carboxamide



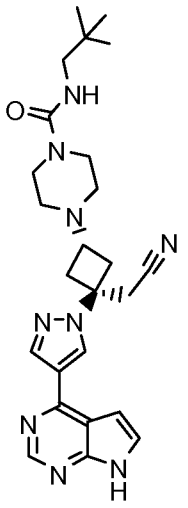
To a solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, from Step 1 of Example 1b) in acetonitrile (1 mL) was added 1.89 M phosgene in toluene (0.032 mL, 0.061 mmol) followed by N,N-diisopropylethylamine (0.011 mL, 0.061 mmol). When formation of the carbamoyl chloride was complete, cyclopropylamine (0.010 g, 0.18 mmol, TCI) was added and the reaction was stirred until deemed complete by LCMS analysis. The solvent was then evaporated. The product was deprotected by stirring in 1:1 TFA:DCM for 1 hour, then ethylenediamine (0.2 mL) in methanol until the deprotection was complete. The product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) to afford the free base (5 mg, 20%). ^1H NMR (300 MHz, CD_3OD) δ 8.70 (s, 1H), 8.66 (s, 1H), 8.39 (s, 1H), 7.50 (d, J = 3.7 Hz, 1H), 6.98 (d, J = 3.7 Hz, 1H), 3.46 – 3.38 (m, 4H), 3.33 (s, 2H), 3.13 – 3.00 (m, 2H), 2.90 (tt, J = 7.0, 7.3 Hz, 1H), 2.59 – 2.43 (m, 3H), 2.43 – 2.31 (m, 4H), 0.69 – 0.60 (m, 2H), 0.48 – 0.39 (m, 2H); LCMS $(M+H)^+$: 446.1.

Example 99. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-cyclobutylpiperazine-1-carboxamide



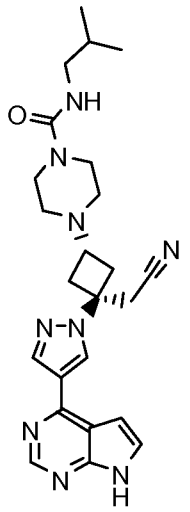
The title compound was prepared according to the method of Example 98, using cyclobutanamine (0.013 g, 0.18 mmol, Aldrich) to afford the product as the free base (5 mg, 20%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.66 (s, 1H), 8.64 (s, 1H), 8.36 (s, 1H), 7.50 (d, J = 3.7 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 4.22 – 4.12 (m, 1H), 3.45 – 3.37 (m, 4H), 3.34 (s, 2H), 2.94 (tt, J = 7.0, 7.2 Hz, 1H), 2.85 – 2.73 (m, 2H), 2.73 – 2.58 (m, 2H), 2.47 – 2.30 (m, 4H), 2.23 (dtt, J = 8.7, 7.3, 2.8 Hz, 2H), 2.00 – 1.86 (m, 2H), 1.72 – 1.57 (m, 2H); LCMS $(M+H)^+$: 460.1.

Example 100. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-(2,2-dimethylpropyl)piperazine-1-carboxamide



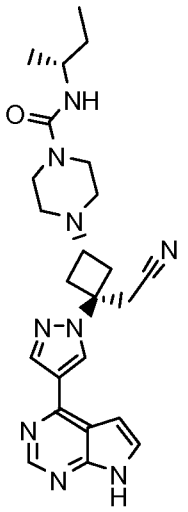
To a solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, from Step 1 of Example 1b) in acetonitrile (1 mL) was added 1.89 M phosgene in toluene (0.035 mL, 0.067 mmol) followed by N,N-diisopropylethylamine (0.011 mL, 0.061 mmol). When formation of carbamoyl chloride was complete, neopentylamine (0.016 g, 0.18 mmol, TCI) was added. When urea formation was complete, solvents were evaporated. The crude product was then stirred with 1:1 TFA in DCM for 1 hour, evaporated and stirred with ethylenediamine (0.2 mL) in methanol until the deprotection was complete. The product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) to afford the free base (6 mg, 20%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.39 (s, 1H), 7.50 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 6.40 (t, J = 6.2 Hz, 1H), 3.49 – 3.41 (m, 4H), 3.33 (s, 2H), 3.11 – 3.02 (m, 2H), 2.99 (d, 2H), 2.91 (tt, J = 7.2, 7.3 Hz, 1H), 2.55 – 2.44 (m, 2H), 2.44 – 2.30 (m, 4H), 0.86 (s, 9H); LCMS $(M+H)^+$: 476.3.

Example 101. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-isobutylpiperazine-1-carboxamide



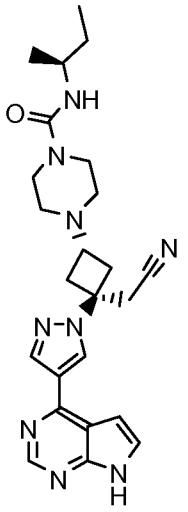
The title compound was prepared according to the procedure of Example 100, using{trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.020 g, 0.040 mmol, from Step 1 of Example 1b), 1.89 M phosgene in toluene (0.030 mL, 0.057 mmol), N,N-diisopropylethylamine (0.0078 mL, 0.045 mmol) and 2-methyl-1-propanamine (9 mg, 0.12 mmol, Aldrich). Purification via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) afforded product as the free base (5 mg, 30%). ^1H NMR (400 MHz, CD_3OD) δ 8.72 (s, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.51 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 3.49 – 3.41 (m, 4H), 3.33 (s, 2H), 3.11 – 3.02 (m, 2H), 2.95 (d, J = 7.1 Hz, 2H), 2.91 (tt, J = 7.1, 7.4 Hz, 1H), 2.55 – 2.45 (m, 2H), 2.44 – 2.36 (m, 4H), 1.75 (hept, J = 6.5 Hz, 1H), 0.88 (d, J = 6.7 Hz, 6H); LCMS $(M+H)^+$: 462.1.

Example 102. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1R)-1-methylpropyl]piperazine-1-carboxamide



The title compound was prepared by the method of Example 101 using (2R)-butan-2-amine (9 mg, 0.12 mmol, Aldrich) to afford product as the free base (7 mg, 40%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.51 (d, *J* = 3.6 Hz, 1H), 6.98 (d, *J* = 3.6 Hz, 1H), 3.67 (h, *J* = 6.6 Hz, 1H), 3.47 – 3.39 (m, 4H), 3.33 (s, 2H), 3.12 – 3.01 (m, 2H), 2.90 (tt, *J* = 7.2, 7.2 Hz, 1H), 2.55 – 2.43 (m, 2H), 2.43 – 2.34 (m, 4H), 1.53 – 1.38 (m, 2H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); LCMS $(M+H)^+$: 462.2.

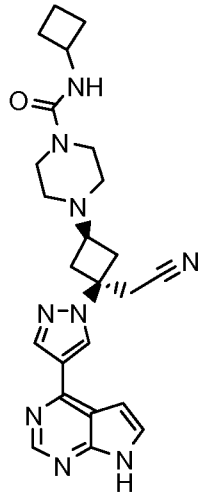
Example 103. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1S)-1-methylpropyl]piperazine-1-carboxamide



The title compound was prepared by the method of Example 101 using (2S)-

butan-2-amine (9 mg, 0.12 mmol, Aldrich) to afford product as the free base (7 mg, 40%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.51 (d, *J* = 3.6 Hz, 1H), 6.98 (d, *J* = 3.6 Hz, 1H), 3.68 (hept, *J* = 6.6, 6.2 Hz, 1H), 3.50 – 3.40 (m, 4H), 3.33 (s, 2H), 3.13 – 3.00 (m, 2H), 2.90 (tt, *J* = 7.1, 7.2 Hz, 1H), 2.55 – 2.44 (m, 2H), 2.42 – 2.35 (m, 4H), 1.54 – 1.36 (m, 2H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); LCMS $(M+H)^+$: 462.2.

Example 104. 4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-cyclobutylpiperazine-1-carboxamide

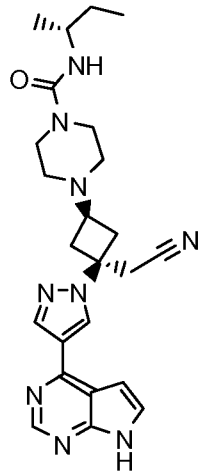


To a solution of {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.040 g, 0.081 mmol, from Step 9 of Example 1a) in methylene chloride (2.0 mL) was added 1.89 M phosgene in toluene (0.0472 mL, 0.0893 mmol). After 15 minutes, cyclobutanamine (0.029 g, 0.40 mmol, Aldrich) was added. When reaction was deemed complete by LCMS, TFA was added (1 mL) and stirred for 1 hour. Solvents were then evaporated and the residue was dissolved in MeOH and ethylenediamine (0.2 mL) was added. When deprotection was complete, the reaction was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH. Eluent containing product was frozen and lyophilized to afford product as the free base (0.01 g, 30%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.65 (s, 1H), 8.63 (s, 1H), 8.36 (s, 1H), 7.50 (d, *J* = 3.7 Hz, 1H), 6.97 (d, *J* = 3.6 Hz, 1H), 4.23 – 4.08 (m, 1H), 3.45 – 3.36 (m, 4H), 3.33 (s, 2H),

2.94 (tt, J = 7.7, 7.8 Hz, 1H), 2.83 – 2.74 (m, 2H), 2.73 – 2.56 (m, 2H), 2.44 – 2.30 (m, 4H), 2.28 – 2.13 (m, 2H), 2.00 – 1.85 (m, 2H), 1.72 – 1.55 (m, 2H).

LCMS $(M+H)^+$: 460.3.

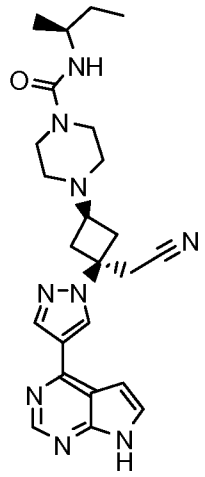
Example 105. 4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1R)-1-methylpropyl]piperazine-1-carboxamide



The procedure of Example 104 was followed, using (2R)-butan-2-amine (30. mg, 0.40 mmol, Aldrich) to afford product as the free base (0.01 g, 30%).

^{1}H NMR (400 MHz, CD_3OD) δ 8.66 (s, 1H), 8.64 (s, 1H), 8.37 (s, 1H), 7.50 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 3.7 Hz, 1H), 3.67 (h, J = 6.7 Hz, 1H), 3.46 – 3.37 (m, 4H), 3.34 (s, 2H), 2.95 (tt, J = 7.6, 7.7Hz, 1H), 2.80 (ddd, J = 9.9, 6.9, 2.9 Hz, 2H), 2.69 (ddd, J = 10.7, 8.0, 2.3 Hz, 2H), 2.48 – 2.33 (m, 4H), 1.56 – 1.34 (m, 2H), 1.10 (d, J = 6.6 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H); LCMS $(M+H)^+$: 462.3.

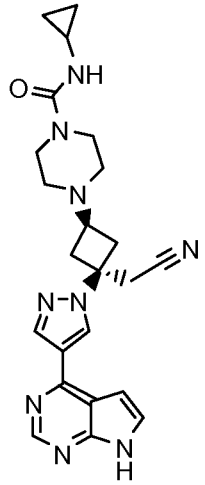
Example 106. 4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1S)-1-methylpropyl]piperazine-1-carboxamide



The procedure of Example 104 was followed, using (2S)-butan-2-amine (30. mg, 0.40 mmol, Aldrich) to afford product as the free base (0.01 g, 30%).

^{1}H NMR (400 MHz, CD_3OD) δ 8.66 (s, 1H), 8.64 (s, 1H), 8.37 (s, 1H), 7.50 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 3.67 (h, J = 6.7 Hz, 1H), 3.47 – 3.37 (m, 4H), 3.34 (s, 2H), 2.95 (tt, J = 7.5, 7.6 Hz, 1H), 2.80 (ddd, J = 9.8, 7.1, 2.6 Hz, 2H), 2.74 – 2.62 (m, 2H), 2.45 – 2.30 (m, 4H), 1.54 – 1.36 (m, 2H), 1.10 (d, J = 6.6 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H); LCMS $(M+H)^+$: 462.2.

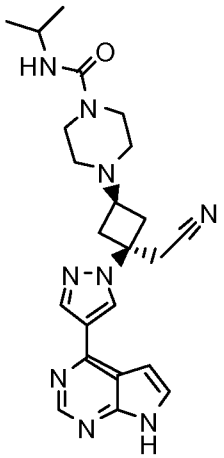
Example 107. 4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-cyclopropylpiperazine-1-carboxamide



The procedure of Example 104 was followed, using cyclopropylamine (23 mg,

0.40 mmol, TCI) to afford product as the free base (0.005 g, 14%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.65 (s, 1H), 8.63 (s, 1H), 8.36 (s, 1H), 7.49 (d, J = 3.6 Hz, 1H), 6.96 (d, J = 3.7 Hz, 1H), 3.43 – 3.35 (m, 4H), 3.33 (s, 2H), 2.93 (tt, J = 7.6, 7.7 Hz, 1H), 2.79 (ddd, J = 9.7, 7.0, 2.5 Hz, 2H), 2.72 – 2.62 (m, 2H), 2.52 (tt, J = 7.1, 3.7 Hz, 1H), 2.42 – 2.34 (m, 4H), 0.64 (td, J = 6.9, 4.9 Hz, 2H), 0.46 – 0.40 (m, 2H); LCMS $(M+H)^+$: 446.1.

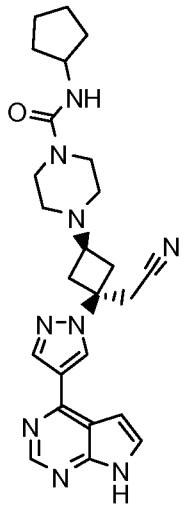
Example 108. 4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-isopropylpiperazine-1-carboxamide



To a solution of {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.040 g, 0.081 mmol, from Step 9 of Example 1a) in methylene chloride (1 mL) was added 2-isocyanatopropane (16 μL, 0.16 mmol, Aldrich) and the reaction was stirred for 2 hours. Methanol was added and then solvents were removed *in vacuo*. The crude product was deprotected by stirring in 1:1 TFA:DCM for 1 hour, followed by evaporation and stirring with ethylenediamine (0.2 mL) in methanol until the deprotection was complete. The product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH). Eluent containing the product was frozen and lyophilized to afford the free base (0.009 g, 20%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.65 (s, 1H), 8.64 (s, 1H), 8.36 (s, 1H), 7.50 (d, J = 3.6 Hz, 1H), 6.97 (d, J = 3.6 Hz, 1H), 3.87 (hept, J = 6.7 Hz, 1H), 3.45 – 3.36 (m, 4H),

3.33 (s, 2H), 2.94 (tt, J = 7.6, 7.7 Hz, 1H), 2.80 (ddd, J = 9.6, 7.0, 2.4 Hz, 2H), 2.73 – 2.59 (m, 2H), 2.44 – 2.36 (m, 4H), 1.12 (d, J = 6.6 Hz, 6H); LCMS $(M+H)^+$: 448.2.

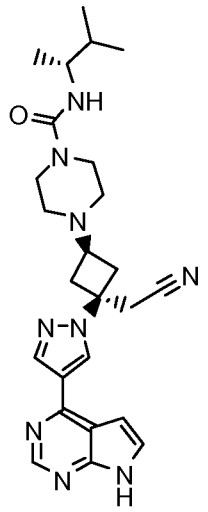
Example 109. 4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-cyclopentylpiperazine-1-carboxamide



The procedure of Example 108 was followed, using isocyanatocyclopentane (18 μL, 0.16 mmol, Aldrich) to afford product as the free base (7 mg, 18%).

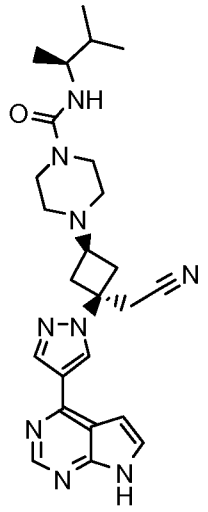
^{1}H NMR (400 MHz, CD_3OD) δ 8.66 (s, 1H), 8.64 (s, 1H), 8.36 (s, 1H), 7.50 (d, J = 3.6 Hz, 1H), 6.97 (d, J = 3.6 Hz, 1H), 3.99 (p, J = 7.3 Hz, 1H), 3.45 – 3.38 (m, 4H), 3.33 (s, 2H), 2.94 (tt, J = 7.6, 7.7 Hz, 1H), 2.80 (ddd, J = 9.6, 7.0, 2.6 Hz, 2H), 2.72 – 2.62 (m, 2H), 2.54 – 2.20 (m, 4H), 1.97 – 1.84 (m, 2H), 1.76 – 1.62 (m, 2H), 1.62 – 1.48 (m, 2H), 1.48 – 1.36 (m, 2H); LCMS $(M+H)^+$: 474.2.

Example 110. 4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1R)-1,2-dimethylpropyl]piperazine-1-carboxamide



The procedure of Example 104 was followed, using (2R)-3-methylbutan-2-amine (0.045 mL, 0.40 mmol, Aldrich) to afford product as the free base (5 mg, 10%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.66 (s, 1H), 8.65 (s, 1H), 8.37 (s, 1H), 7.51 (d, J = 3.6 Hz, 1H), 6.99 (d, J = 3.6 Hz, 1H), 6.11 (d, J = 8.5 Hz, 1H), 3.64 – 3.53 (m, 1H), 3.47 – 3.38 (m, 4H), 3.34 (s, 2H), 2.96 (tt, J = 7.5, 7.5 Hz, 1H), 2.81 (ddd, J = 9.9, 7.0, 2.8 Hz, 2H), 2.75 – 2.63 (m, 2H), 2.46 – 2.36 (m, 4H), 1.67 (h, J = 6.8 Hz, 1H), 1.08 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H); LCMS $(M+H)^+$: 476.2.

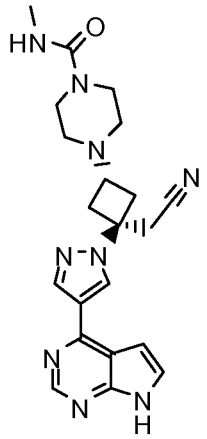
Example 111. 4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1S)-1,2-dimethylpropyl]piperazine-1-carboxamide



The procedure of Example 104 was followed, using (2S)-3-methylbutan-2-amine

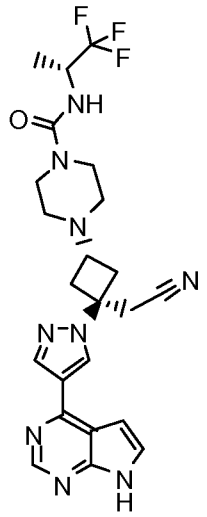
(0.035 g, 0.40 mmol, Alfa Aesar) to afford product as the free base (5 mg, 10%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.66 (s, 1H), 8.65 (s, 1H), 8.37 (s, 1H), 7.51 (d, *J* = 3.6 Hz, 1H), 6.99 (d, *J* = 3.7 Hz, 1H), 6.11 (d, *J* = 8.4 Hz, 1H), 3.64 – 3.52 (m, 1H), 3.46 – 3.39 (m, 4H), 3.34 (s, 2H), 2.96 (tt, *J* = 7.2, 7.2 Hz, 1H), 2.86 – 2.73 (m, 2H), 2.74 – 2.63 (m, 2H), 2.46 – 2.35 (m, 4H), 1.66 (dq, *J* = 13.6, 6.8 Hz, 1H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H); LCMS $(M+H)^+$: 476.2.

Example 112. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-methylpiperazine-1-carboxamide



The procedure of Example 108 was followed, using {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, from Step 1 of Example 1b) and Methyl Isocyanate (3.98 μL, 0.0670 mmol, Supelco) to yield product as the free base (0.02 g, 80%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.39 (s, 1H), 7.51 (d, *J* = 3.6 Hz, 1H), 6.98 (d, *J* = 3.6 Hz, 1H), 3.48 – 3.38 (m, 4H), 3.33 (s, 2H), 3.14 – 3.00 (m, 2H), 2.90 (tt, *J* = 6.3, 6.7 Hz, 1H), 2.70 (s, 3H), 2.58 – 2.43 (m, 2H), 2.43 – 2.33 (m, 4H); LCMS $(M+H)^+$: 420.1.

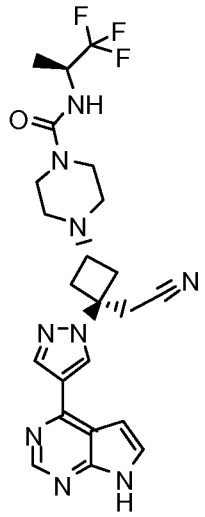
Example 113. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1R)-2,2,2-trifluoro-1-methylethyl]piperazine-1-carboxamide



To a solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.040 g, 0.081 mmol, from Step 1 of Example 1b) in methylene chloride (1.0 mL) was added 1.89 M phosgene in toluene (0.0472 mL, 0.0893 mmol) and this was stirred for 15 minutes. During this time a mixture of (2R)-1,1,1-trifluoropropan-2-amine hydrochloride (0.024 g, 0.16 mmol, Synquest) and N,N-diisopropylethylamine (0.028 mL, 0.16 mmol) in methylene chloride (1.0 mL) was prepared, which was then added to the mixture of starting material and phosgene. The reaction vial was sealed and heated at a temperature of 50 °C for an hour, then stood at room temperature overnight. Methanol was added and then the solvents were evaporated to dryness with a stream of nitrogen. The residue was reconstituted in MeCN and 1N NaOH, filtered and purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH). Eluent containing the product was evaporated. The product was deprotected by stirring with 4 mL of TFA:DCM (1:1) for 2 hours. Solvents were evaporated and the residue was dissolved in methanol. Ethylenediamine (0.2 mL) was added. After 1 hour, the product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) to afford product as the free base (1.2 mg, 3%). LCMS $(M+H)^+$: 502.1.

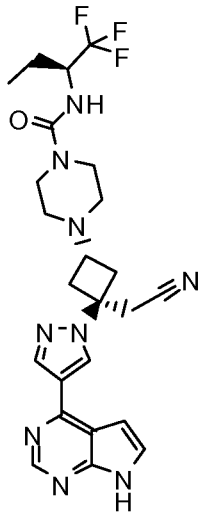
Example 114. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-

pyrazol-1-yl]cyclobutyl}-N-[(1S)-2,2,2-trifluoro-1-methylethyl]piperazine-1-carboxamide



The title compound was prepared by the method of Example 113, using (2S)-1,1,1-trifluoropropan-2-amine hydrochloride (0.024 g, 0.16 mmol, Synquest) to afford product as the free base (1.9 mg, 5%). LCMS $(M+H)^+$: 502.0.

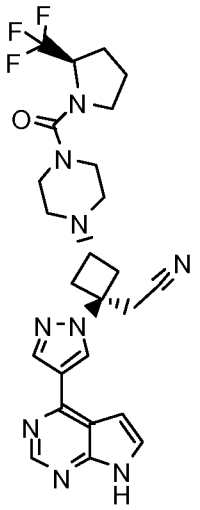
Example 115. 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1S)-1-(trifluoromethyl)propyl]piperazine-1-carboxamide



To a solution of (2S)-1,1,1-trifluorobutan-2-amine (0.050 g, 0.39 mmol, Oakwood) in methylene chloride (1 mL) was added pyridine (32 μL, 0.39 mmol) and p-

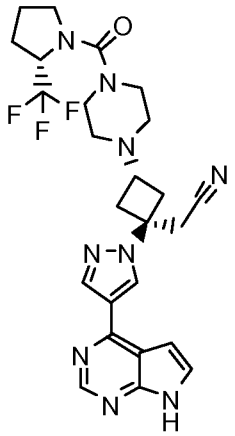
nitrophenyl chloroformate (0.087 g, 0.43 mmol). After stirring overnight, the reaction mixture was partitioned between water and ethyl acetate, and the aqueous portion was extracted with a further two portions of ethyl acetate. The combined extracts were dried over sodium sulfate, decanted and concentrated. The crude product was dissolved in 1,4-dioxane (1 mL) and {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.060 g, 0.12 mmol, from Step 1 of Example 1b) and N,N-diisopropylethylamine (42 μL, 0.24 mmol) were then added. The mixture was heated to 60 °C for 1 hour, then cooled to room temperature. The dioxane was removed *in vacuo*. The residue was stirred with 1:1 TFA:DCM for 1 hour, then with 0.2 mL ethylenediamine in methanol until the deprotection was complete. The product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH). The eluent was frozen and lyophilized to afford product as the free base (0.01 g, 16%). ^{1}H NMR (400 MHz, dmso) δ 12.11 (br s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 6.75 (d, J = 8.7 Hz, 1H), 4.42 – 4.09 (m, 1H), 3.42 (s, 2H), 3.41 – 3.35 (m, 4H), 3.06 – 2.93 (m, 2H), 2.78 (tt, J = 7.2, 7.3 Hz, 1H), 2.42 – 2.31 (m, 2H), 2.31 – 2.20 (m, 4H), 1.76 – 1.48 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H); ^{19}F NMR (376 MHz, dmso) δ -75.22 (d, J = 8.3 Hz); LCMS $(M+H)^+$: 516.3.

Example 116. [trans-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[(2R)-2-(trifluoromethyl)pyrrolidin-1-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile



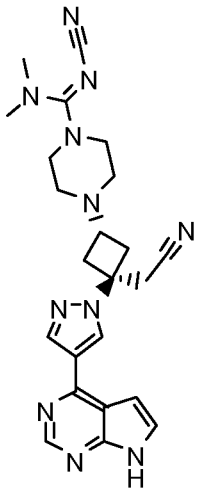
A solution of (2R)-2-(trifluoromethyl)pyrrolidine (0.013 g, 0.091 mmol, Aldrich) and N,N-carbonyldiimidazole (0.015 g, 0.091 mmol) in methylene chloride (0.4 mL) and tetrahydrofuran (0.1 mL) was stirred overnight. A solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.030 g, 0.061 mmol, from Step 1 of Example 1b) in Tetrahydrofuran (0.2 mL) was then added. Stirring was continued for 96 hours at room temperature. The reaction was then heated to 70 °C in a sealed vial overnight, then to 90 °C for 3 hours. After cooling, solvent was removed *in vacuo* and the residue was deprotected by stirring with 1:1 TFA:DCM for 1 hour, followed by evaporation and stirring with 0.2 mL ethylenediamine in methanol until the deprotection was complete. The product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH). The eluent was frozen and lyophilized to afford product as the free base (2 mg, 6%). ^1H NMR (500 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.84 (s, 1H), 8.47 (s, 1H), 8.33 (s, 1H), 7.39 – 7.33 (m, 1H), 6.85 – 6.74 (m, 1H), 5.07 – 4.67 (m, 1H), 3.65 – 1.74 (m, 21H); LCMS $(M+H)^+$: 528.4.

Example 117. [trans-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[(2S)-2-(trifluoromethyl)pyrrolidin-1-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile



The title compound was prepared as described for Example 116, using (2S)-2-(trifluoromethyl)pyrrolidine (0.013 g, 0.091 mmol, Aldrich) to afford product as free base (3 mg, 9%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.84 (s, 1H), 8.47 (s, 1H), 8.33 (s, 1H), 7.38 (dd, J = 3.7, 2.2 Hz, 1H), 6.81 (dd, J = 3.6, 1.8 Hz, 1H), 4.99 – 4.90 (m, 1H), 3.64 – 3.45 (m, 2H), 3.43 – 3.30 (m, 4H), 3.23 (s, 2H), 3.12 – 2.83 (m, 3H), 2.61 – 2.23 (m, 6H), 2.24 – 2.07 (m, 1H), 2.06 – 1.88 (m, 2H), 1.88 – 1.74 (m, 1H); LCMS $(M+H)^+$: 528.4.

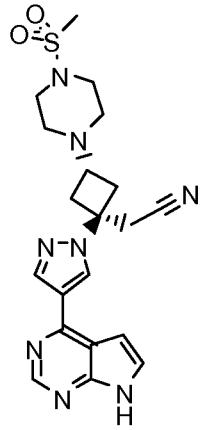
Example 118. N'-cyano-4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N,N-dimethylpiperazine-1-carboximidamide



To {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.025 g, 0.051

mmol, from Step 1 of Example 1b) in tetrahydrofuran (0.5 mL) was added diphenyl cyanocarbonimidate (0.0121 g, 0.0507 mmol, Aldrich). After stirring overnight, 2.0 M dimethylamine in THF (0.5 mL, 1 mmol, Aldrich) was added and the reaction was stirred for 2 hours. Solvent was removed *in vacuo*. The crude product was stirred with 1:1 TFA:DCM for 1 hour, solvent was again evaporated, and the residue was stirred with NH_4OH in methanol overnight. The product was purified via preparative HPLC-MS (C18 eluting with a gradient of $MeCN/H_2O$ containing 0.15% NH_4OH) and was afforded as the free base (2 mg, 9%). ^1H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.51 (d, J = 3.7 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 3.53 – 3.42 (m, 4H), 3.35 (s, 2H), 3.11 – 3.02 (m, 2H), 2.99 (s, 6H), 2.99-2.91 (m, 1H), 2.57 – 2.44 (m, 6H); LCMS $(M+H)^+$: 458.1.

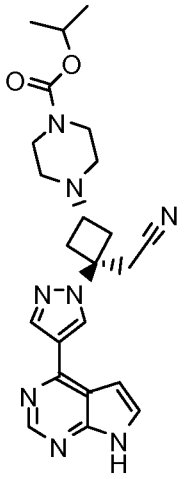
Example 119. {trans-3-[4-(methylsulfonyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



The title compound was obtained as a byproduct during Step E of Example 47, due to impurity resulting from incomplete amide formation in the previous step (Step D). The byproduct was isolated using preparative HPLC-MS (C18 eluting with a gradient of $MeCN/H_2O$ containing 0.15% NH_4OH) in the amount of 3 mg.

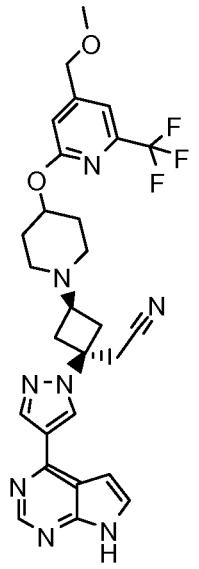
^1H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1H), 8.66 (s, 1H), 8.40 (s, 1H), 7.51 (d, J = 3.6 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 3.33 (s, 2H), 3.28 – 3.23 (m, 4H), 3.11 – 3.02 (m, 2H), 2.96 (tt, J = 7.1, 7.1 Hz, 1H), 2.85 (s, 3H), 2.58 – 2.44 (m, 6H); LCMS $(M+H)^+$: 441.0.

Example 120. isopropyl 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazine-1-carboxylate



To a solution of {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.040 g, 0.081 mmol, from Step 1 of Example 1b) in methylene chloride (1 mL) was added triethylamine (0.023 mL, 0.16 mmol) followed by 1.0 M isopropyl chloroformate in toluene (0.097 mL, 0.097 mmol, Aldrich) . The reaction was stirred for 2 hours. Methanol was added to the reaction, then solvent was removed *in vacuo*. The crude product was stirred with 1:1 TFA:DCM for 1 hour, then with excess ethylenediamine in methanol until the deprotection was complete. The product was purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) to yield 0.01 g (30%). ^{1}H NMR (400 MHz, dmso) δ 12.13 (s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.41 (s, 1H), 7.60 (dd, J = 3.6, 2.3 Hz, 1H), 7.07 (dd, J = 3.6, 1.6 Hz, 1H), 4.76 (hept, 1H), 3.42 (s, 2H), 3.38 – 3.32 (m, 4H), 3.06 – 2.94 (m, 2H), 2.83 – 2.71 (m, 1H), 2.40 – 2.30 (m, 2H), 2.30 – 2.17 (m, 4H), 1.17 (d, J = 6.2 Hz, 6H); LCMS $(M+H)^+$: 449.2.

Example 121. {cis-3-(4-{[4-(methoxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (single isomer isolated)



Step A. [2-Chloro-6-(trifluoromethyl)pyridin-4-yl]methanol

Sodium tetrahydroborate (74 mg, 2.0 mmol) was added to a solution of ethyl 2-chloro-6-(trifluoromethyl)isonicotinate (0.50 g, 2.0 mmol, Anichem) in ethanol (17 mL) at 0 °C. The mixture was stirred at 0 °C for one hour, then was allowed to warm to room temperature and stir for 2 hours. The mixture was recooled in an ice bath and was quenched by the dropwise addition of 4.0 mL 1N HCl. The pH was then adjusted to 7 by the addition of saturated sodium bicarbonate solution. The reaction was further diluted with water, and then was extracted with EtOAc. The extract was washed with brine, dried over sodium sulfate, filtered and concentrated. Flash chromatography on silica gel, eluting with a gradient from 0-40% EtOAc in Hexanes afforded product as an oil (0.33 g, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.56 (s, 1H), 4.84 (d, J = 5.2 Hz, 2H), 2.20 (t, J = 5.6 Hz, 1H); LCMS $(M+H)^+$: 212.1.

Step B. 2-Chloro-4-(methoxymethyl)-6-(trifluoromethyl)pyridine

To a solution of [2-chloro-6-(trifluoromethyl)pyridin-4-yl]methanol (130 mg, 0.614 mmol, from Step A) and methyl iodide (42 μL, 0.68 mmol) in N,N-dimethylformamide (0.65 mL, 8.4 mmol) was added potassium carbonate (250 mg, 1.8 mmol). The mixture was sealed and stirred at room temperature for 24 hours. Additional methyl iodide (42 μL, 0.68 mmol) was added. The mixture was stirred again for 24 hours, then was diluted with water and extracted with EtOAc. The extract was washed with

water (3x), followed by brine, dried over sodium sulfate, filtered and concentrated. Flash chromatography on silica gel, eluting with a gradient from 0-20% EtOAc in Hexanes, afforded product as a colorless oil (56 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.50 (s, 1H), 4.53 (s, 2H), 3.48 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -68.45 (s); LCMS $(M+H)^+$: 226.1.

Step C. tert-Butyl 4-{[4-(methoxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidine-1-carboxylate

To sodium hydride (18 mg, 0.45 mmol, 60% in mineral oil) in tetrahydrofuran (0.50 mL) was added tert-butyl 4-hydroxypiperidine-1-carboxylate (91 mg, 0.45 mmol, Aldrich). The mixture was stirred for 45 minutes, followed by the addition of 2-chloro-4-(methoxymethyl)-6-(trifluoromethyl)pyridine (51 mg, 0.23 mmol, from Step B) in tetrahydrofuran (0.30 mL). The vial was sealed and stirred at room temperature overnight. The mixture was quenched and diluted with water and extracted with EtOAc. The extract was washed with water, brine, dried over sodium sulfate, filtered and concentrated. Flash chromatography on silica gel, eluting with a gradient from 0-10% EtOAc in hexanes afforded product as an oil (42 mg, 48%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (s, 1H), 6.85 (s, 1H), 5.26 (tt, J = 7.7, 4.0 Hz, 1H), 4.46 (s, 2H), 3.73 (dq, J = 11.1, 3.9 Hz, 2H), 3.44 (s, 3H), 3.32 (ddd, J = 13.6, 8.3, 3.7 Hz, 2H), 1.98 (ddq, J = 10.3, 6.9, 3.5 Hz, 2H), 1.73 (ddt, J = 16.0, 7.5, 3.6 Hz, 2H), 1.47 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -68.88 (s); LCMS $(M-tBu+H)^+$: 335.1.

Step D. 4-(Methoxymethyl)-2-(piperidin-4-yloxy)-6-(trifluoromethyl)pyridine

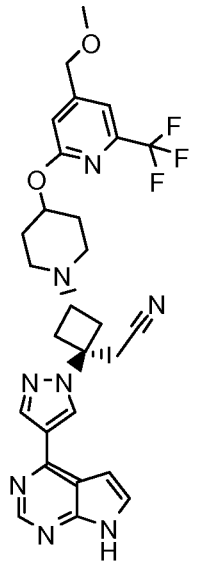
To a solution of tert-butyl 4-{[4-(methoxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidine-1-carboxylate (40. mg, 0.10 mmol, from Step C) in Methylene chloride (1.0 mL) was added 4.0 M Hydrogen chloride in dioxane (0.50 mL, 2.0 mmol). The reaction mixture was stirred for one hour. The solvent was removed *in vacuo*. The residue was dissolved in DCM, and this solution was washed with saturated sodium bicarbonate, water (2x), brine, dried over sodium sulfate, filtered and concentrated to give product which was used without further purification (30 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.18 (s, 1H), 6.84 (s, 1H), 5.19 (tt, J = 8.4, 3.6 Hz, 1H), 4.45 (s, 2H), 3.44 (s, 3H), 3.19 – 3.03 (m, 2H), 2.88 – 2.70 (m, 2H), 2.13 – 1.97 (m, 2H), 1.73 – 1.53 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.89 (s); LCMS $(M+H)^+$: 291.1.

Step E. {cis-3-(4-{[4-(Methoxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (single isomer)

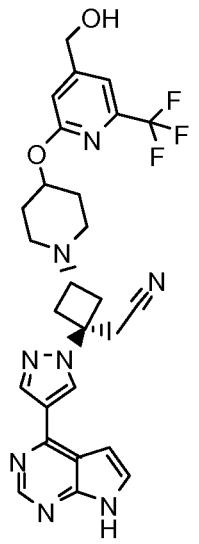
Sodium cyanoborohydride (7.8 mg, 0.12 mmol) and zinc dichloride (8.4 mg, 0.062 mmol) were precombined in methanol (0.5 mL) and stirred for 2 hours, according to the procedure found in JOC 1985, 50, 1927-1932. Following this, {3-oxo-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (58 mg, 0.12 mmol, from Step 7 of Example 1a) and 4-(methoxymethyl)-2-(piperidin-4-yloxy)-6-(trifluoromethyl)pyridine (30. mg, 0.10 mmol, from Step D) in methanol (0.9 mL, 20 mmol) was stirred to dissolve and then the reducing solution generated from the zinc dichloride and sodium cyanoborohydride was added. The reaction was stirred overnight. Purification via preparative HPLC-MS (Waters XBridge C18, 30 x 100 mm, eluting with a gradient from 53.8% to 71.8% MeCN/H_2O containing 0.15% NH_4OH over 12 min at 60 mL/min) afforded two SEM protected isomers: Peak 1, 1st peak eluted (LCMS $(M+H)^+$: 697.4), 13.6 mg; Peak 2, 2nd peak eluted (LCMS $(M+H)^+$: 697.4), 13.9 mg. Peak 1 was deprotected by stirring with 1:1 TFA/DCM for one hour, removal of solvents, then stirring in 1.0 mL MeOH containing 0.10 mL ethylenediamine until deprotection was complete. Purification via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) afforded the cis product as the free base (6.7 mg, 11%). Peak 1: cis, ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.80 (s, 1H), 8.28 (s, 1H), 8.24 (s, 1H), 7.35 (dd, J = 3.7, 2.1 Hz, 1H), 7.24 (s, 1H), 7.16 (s, 1H), 6.82 (s, 1H), 6.75 – 6.68 (m, 1H), 5.17-5.10 (m, 1H), 4.43 (s, 2H), 3.42 (s, 3H), 3.12 (s, 2H), 2.90 (tt, J = 7.4, 7.5 Hz, 1H), 2.83 – 2.71 (m, 4H), 2.66 (br m, 2H), 2.28 (br m, J = 11.1 Hz, 2H), 2.11 – 1.99 (m, 2H), 1.90 – 1.75 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -69.01 (s); LCMS $(M+H)^+$: 567.2.

Example 122. {trans-3-(4-{[4-(methoxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (single isomer)



The title compound was prepared by the method of Example 121, Step E using Peak 2 from separation of the SEM-protected intermediates in that step, to afford product as the free base (7.2 mg, 12%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.98 (s, 1H), 8.87 (s, 1H), 8.50 (s, 1H), 8.36 (s, 1H), 7.43 (dd, J = 3.7, 2.0 Hz, 1H), 7.18 (s, 1H), 6.84 (s, 1H), 6.81 (dd, J = 3.6, 1.6 Hz, 1H), 5.17-5.10 (m, 1H), 4.45 (s, 2H), 3.43 (s, 3H), 3.23 (s, 2H), 3.07 – 2.99 (m, 2H), 2.94 (tt, J = 6.8, 6.9 Hz, 1H), 2.66 (br m, 2H), 2.53 – 2.41 (m, 2H), 2.27 (br m, J = 10.5 Hz, 2H), 2.13 – 2.03 (m, 2H), 1.88 – 1.75 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.93 (s); LCMS $(M+H)^+$: 567.2.

Example 123. {trans-3-(4-{[4-(hydroxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (single isomer isolated)



Step A. 4-({[tert-Butyl(diphenyl)silyl]oxy}methyl)-2-chloro-6-(trifluoromethyl)pyridine

To a solution of [2-chloro-6-(trifluoromethyl)pyridin-4-yl]methanol (142 mg, 0.671 mmol, Example 121, Step A) in methylene chloride (1.0 mL) at 0 °C was added 1H-imidazole (55 mg, 0.80 mmol) followed by tert-Butylchlorodiphenylsilane (190 μL, 0.74 mmol) and 4-dimethylaminopyridine (4 mg, 0.03 mmol). The reaction was stirred with warming to room temperature for 64 hours. The reaction mixture was diluted with diethyl ether and was washed with water followed by brine, dried over sodium sulfate, decanted and concentrated. Flash chromatography on silica gel, eluting with a gradient from 0-4% EtOAc in hexanes afforded product as a white solid (0.20 g, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.58 (m, 4H), 7.55 – 7.34 (m, 8H), 4.77 (s, 2H), 1.12 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -68.49 (s); LCMS $(M+H)^+$: 450.1.

Step B. tert-Butyl 4-{[4-({[tert-butyl(diphenyl)silyl]oxy}methyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidine-1-carboxylate

To sodium hydride (36 mg, 0.89 mmol, 60% in mineral oil) in tetrahydrofuran (1.0 mL) was added tert-butyl 4-hydroxypiperidine-1-carboxylate (0.18 g, 0.89 mmol, Aldrich). After stirring for 45 minutes, 4-({[tert-butyl(diphenyl)silyl]oxy}methyl)-2-chloro-6-(trifluoromethyl)pyridine (0.20 g, 0.44 mmol, from Step A) in tetrahydrofuran (0.60 mL) was added and the mixture was stirred overnight. The reaction was quenched and diluted with water and extracted with ether. The extract was washed with

water, brine, dried over sodium sulfate, filtered and concentrated. Flash chromatography on silica gel, eluting with a gradient from 0-5% EtOAc in hexanes afforded product as an oil (0.19 g, 52%). LCMS $(M\text{-}tBu+H)^+$: 559.2

Step C. 4-({[tert-Butyl(diphenyl)silyl]oxy}methyl)-2-(piperidin-4-yloxy)-6-(trifluoromethyl)pyridine

To a solution of tert-butyl 4-{[4-({[tert-butyl(diphenyl)silyl]oxy}methyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidine-1-carboxylate (0.19 g, 0.23 mmol, from Step B) in 1,4-dioxane (2.0 mL) was added 4.0 M hydrogen chloride in dioxane (0.50 mL, 2.0 mmol). The reaction mixture was stirred for one hour. Additional 4.0 M hydrogen chloride in dioxane (0.50 mL, 2.0 mmol) was added and stirring was continued for two hours. The mixture was diluted with water, saturated sodium bicarbonate was used to adjust the pH to between 7 and 8, and then the product was extracted with two portions of DCM. The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. Flash chromatography on silica gel, eluting with a gradient from 0-15% MeOH in DCM afforded product as an oil (62 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 4H), 7.48 – 7.34 (m, 6H), 7.14 – 7.11 (m, 1H), 6.91 (s, 1H), 5.17 (tt, J = 8.7, 4.0 Hz, 1H), 4.71 (s, 2H), 3.13 (dt, J = 12.7, 4.5 Hz, 2H), 2.78 (ddd, J = 12.7, 9.7, 3.0 Hz, 2H), 2.07 (dq, J = 12.2, 4.1 Hz, 2H), 1.67 (dtd, J = 13.0, 9.4, 3.9 Hz, 2H), 1.11 (s, 9H); LCMS $(M+H)^+$: 515.2.

Step D. {3-(4-{[4-({[tert-Butyl(diphenyl)silyl]oxy}methyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (a mixture of cis- and trans-isomers)

Sodium cyanoborohydride (8.8 mg, 0.14 mmol) and zinc dichloride (9.5 mg, 0.070 mmol) were combined in methanol (0.56 mL, 14 mmol) and stirred for 2 hours to generate the reducing solution referenced in JOC 1985, 50, 1927-1932. Subsequently, {3-oxo-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (66 mg, 0.14 mmol, from Step 7 of Example 1a) and

4-({[tert-butyl(diphenyl)silyl]oxy}methyl)-2-(piperidin-4-yloxy)-6-(trifluoromethyl)pyridine (60. mg, 0.12 mmol, from Step C) were combined in Methanol (2.0 mL) to dissolve, then the above generated reducing mixture was added. The reaction was stirred overnight. An additional 0.3 eq of the prestirred $NaCNBH_3/ZnCl_2$ mixture was added. After stirring for 3 hours, the mixture was diluted with EtOAc and was washed with saturated sodium bicarbonate solution, followed by brine, dried over sodium sulfate, filtered and concentrated. Flash chromatography on silica gel, eluting with a gradient from 0-80% EtOAc in hexanes afforded product as a mixture of cis- and trans-isomers (43 mg, 40%). LCMS $(M+2H)^{2+}$: 461.4.

Step E. {cis-3-(4-{[4-(hydroxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile and {trans-3-(4-{[4-(hydroxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (each diastereomer isolated)

To {3-(4-{[4-({[tert-butyl(diphenyl)silyl]oxy}methyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.35 g, 0.38 mmol, a mixture of cis- and trans- isomers from Step D) in ethanol (10. mL, 180 mmol) was added 5.0 M sodium hydroxide in water (1.5 mL, 7.6 mmol). After stirring for 3 hours, the reaction mixture was partitioned between DCM and brine. The aqueous layer was extracted with an additional portion of DCM. The combined extracts were dried over sodium sulfate, filtered and concentrated. Flash chromatography on silica gel, eluting with a gradient from 0-10% MeOH in DCM afforded a mixture of isomers (0.22 g, 76%). The isomers were separated by chiral HPLC (Phenomenex Lux-Cellulose 2 column, eluting with 45% EtOH in hexanes at 18mL/min, ~44mg/injection). Peak 1 retention time: 6.0 min, Peak 2 retention time: 10.2 min. Peak 1, trans isomer, 83 mg: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.47 (s, 1H), 8.33 (s, 1H), 7.40 (d, J = 3.7 Hz, 1H), 7.21 (s, 1H), 6.89 (s, 1H), 6.81 (d, J = 3.7 Hz, 1H),

5.68 (s, 2H), 5.15 (br m, 1H), 4.73 (s, 2H), 3.61 – 3.45 (m, 2H), 3.22 (s, 2H), 3.08 – 2.97 (m, 2H), 2.97 – 2.84 (m, 1H), 2.67 (br m, 2H), 2.48 (br m, 2H), 2.25 (br m, 2H), 2.07 (br m, 2H), 1.84 (br m, 2H), 0.98 – 0.84 (m, 2H), -0.05 (s, 9H); LCMS $(M+H)^+$: 683.4.

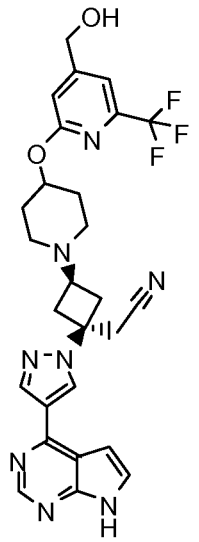
Peak 2, cis isomer, 78 mg: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.39 (s, 1H), 8.29 (s, 1H), 7.39 (d, *J* = 3.7 Hz, 1H), 7.21 (s, 1H), 6.90 (s, 1H), 6.80 (d, *J* = 3.7 Hz, 1H), 5.67 (s, 2H), 5.20 – 5.06 (m, 1H), 4.73 (s, 2H), 3.64 – 3.46 (m, 2H), 3.14 (s, 2H), 2.90 (tt, *J* = 7.4, 7.8 Hz, 1H), 2.84 – 2.76 (m, 2H), 2.75 – 2.52 (m, 4H), 2.28 (br m, 2H), 2.04 (br m, 2H), 1.81 (br m, 2H), 1.69 (s, 2H), 1.01 – 0.81 (m, 2H), -0.06 (s, 9H); LCMS $(M+H)^+$: 683.3.

Step F. {trans-3-(4-{[4-(Hydroxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

{trans-3-(4-{[4-(Hydroxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (30. mg, 0.044 mmol, Peak 1 from Step E) was dissolved in methylene chloride (3.0 mL) and trifluoroacetic acid (3.0 mL, 39 mmol) was added. After stirring for 1.5 hours, the solvent was removed *in vacuo*. The residue was dissolved in 1.0 mL methanol, and 0.10 mL ethylenediamine was added. When deprotection was complete as determined by LCMS, purification via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) afforded product as the free base (18 mg, 75%). ^{1}H NMR (400 MHz, dmso) δ 12.13 (s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (dd, *J* = 3.6, 2.3 Hz, 1H), 7.37 (s, 1H), 7.08 (dd, *J* = 3.6, 1.7 Hz, 1H), 6.99 (s, 1H), 5.57 (t, *J* = 5.8 Hz, 1H), 5.00 (tt, *J* = 8.5, 4.2 Hz, 1H), 4.56 (d, *J* = 5.7 Hz, 2H), 3.42 (s, 2H), 3.09 – 2.93 (m, 2H), 2.81 (tt, *J* = 7.3, 7.3 Hz, 1H), 2.65 (br m, *J* = 11.5 Hz, 2H), 2.41 – 2.28 (m, 2H), 2.17 (br m, 2H), 2.01 (br m, 2H), 1.69 (br m, *J* = 11.1 Hz, 2H); ^{19}F NMR (376 MHz, dmso) δ -67.39 (s); LCMS $(M+H)^+$: 553.2.

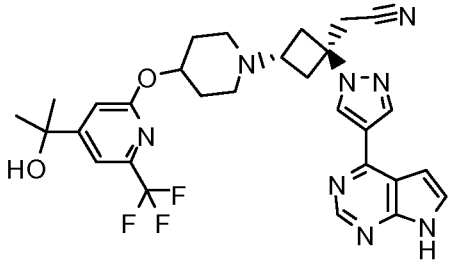
Example 124. {cis-3-(4-{[4-(hydroxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-

yl]cyclobutyl}acetonitrile (single isomer isolated)



The procedure of Example 123, Step F was followed using Peak 2 from Example 123, Step E to afford product as the free base. LCMS $(M+H)^+$: 553.2.

Example 125. {trans-3-(4-{[4-(1-hydroxy-1-methylethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (single isomer isolated)



Step A. 2-[2-Chloro-6-(trifluoromethyl)pyridin-4-yl]propan-2-ol

To a solution of ethyl 2-chloro-6-(trifluoromethyl)isonicotinate (0.200 g, 0.789 mmol, Anichem) in tetrahydrofuran (5 mL) at 0 °C was added 3.0 M methylmagnesium bromide in diethyl ether (0.66 mL, 2.0 mmol). After 30 minutes, the reaction was quenched by the addition of saturated ammonium chloride solution and extracted with three portions of ethyl acetate. The combined extracts were dried over sodium sulfate, decanted and concentrated. Used without further purification in Step B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 1.4 Hz, 1H), 7.66 – 7.59 (m, 1H), 1.59 (s, 6H); ^{19}F NMR

(282 MHz, $CDCl_3$) δ -68.30 (s); LCMS $(M+H)^+$: 240.1.

Step B. 2-[2-(piperidin-4-yloxy)-6-(trifluoromethyl)pyridin-4-yl]propan-2-ol

Tert-butyl 4-hydroxypiperidine-1-carboxylate (0.95 g, 4.7 mmol, Aldrich) was added to Sodium hydride (0.19 g, 4.7 mmol, 60% in mineral oil) in tetrahydrofuran (7 mL, 80 mmol). After stirring for 4 hours additional tetrahydrofuran (5 mL) was added, followed by 2-[2-chloro-6-(trifluoromethyl)pyridin-4-yl]propan-2-ol (0.189 g, 0.789 mmol, from Step A) as a solution in tetrahydrofuran (7 mL). The reaction was heated to 50 °C for 4 hours, then raised to 65 °C and stirred overnight. Upon cooling to room temperature, water was added and the product was extracted with three portions of ethyl acetate. The combined extracts were dried with sodium sulfate, decanted and concentrated. The product was purified via preparative HPLC-MS (C18 eluting with a gradient of $MeCN/H_2O$ containing 0.1% TFA). Intermediate Boc-protected product: ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 6.97 (s, 1H), 5.29 – 5.21 (m, 1H), 3.71 (ddd, *J* = 13.7, 6.9, 3.8 Hz, 2H), 3.30 (ddd, *J* = 13.1, 8.3, 3.6 Hz, 2H), 2.64 (s, 1H), 1.99 – 1.91 (m, 2H), 1.77 – 1.65 (m, 2H), 1.55 (s, 6H), 1.45 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.72 (s).

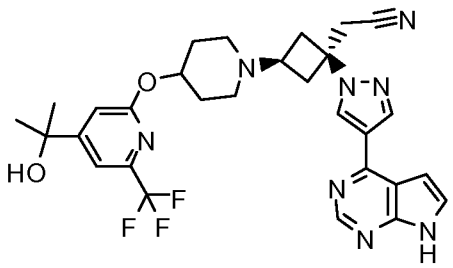
A portion of this product (87 mg) was Boc-deprotected by stirring in 1,4-Dioxane (5 mL) containing 4.0 M Hydrogen chloride in Dioxane (2 mL, 8 mmol) overnight. The reaction mixture was poured into sufficient saturated sodium bicarbonate solution to make the mixture basic. The product was then extracted with four portions of ethyl acetate. The combined extracts were dried over sodium sulfate, decanted and concentrated. LCMS $(M+H)^+$: 305.1.

Step C. {trans-3-(4-{[4-(1-hydroxy-1-methylethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (single isomer isolated)

To zinc dichloride (0.017 g, 0.13 mmol) in methanol (1 mL, 20 mmol) was added sodium cyanoborohydride (0.0161 g, 0.256 mmol) . This solution was stirred for 2 hours and is referred to as Solution A. Then, 2-[2-(piperidin-4-yloxy)-6-

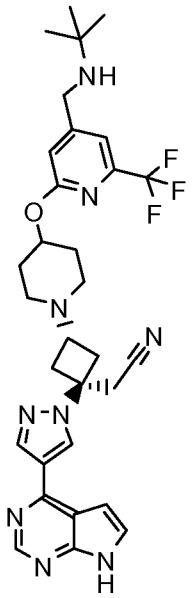
(trifluoromethyl)pyridin-4-yl]propan-2-ol (0.078 g, 0.26 mmol, from Step B) and {3-oxo-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.108 g, 0.256 mmol, from Step 7 of Example 1a) were combined in methanol (2 mL) to form solution B. After a few minutes, solution A was added to solution B and the reaction was stirred for 40 hours. Water was added and the product was extracted with three portions of ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, decanted and concentrated. Flash chromatography on silica gel, eluting with a gradient from 0-10% MeOH/DCM afforded SEM-protected products as a mixture of cis and trans isomers. Chiral HPLC was used to separate the isomers (Phenomenex Lux-Cellulose 2; 30% EtOH/Hx, 22 mL/min, ~22 mg/inj). Retention time of first isomer to elute (Peak 1): 6.65 min; retention time of second isomer to elute (Peak 2): 11.45 min. Peak 1 was stirred with 1:1 TFA:DCM for 1.5 hours, solvents were evaporated, then the residue was stirred with 0.7 mL ethylenediamine in methanol for 2 hours. Purification via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH), followed by lyophilization afforded product as the free base. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.84 (s, 1H), 8.49 (s, 1H), 8.34 (s, 1H), 7.38 (dd, J = 3.7, 1.6 Hz, 1H), 7.33 (d, J = 1.4 Hz, 1H), 6.96 (s, 1H), 6.81 (d, J = 4.0 Hz, 1H), 5.16 (ddd, J = 11.2, 7.4, 3.6 Hz, 1H), 3.23 (s, 2H), 3.07 – 3.00 (m, 2H), 2.94 (tt, J = 6.8, 7.0 Hz, 1H), 2.67 (br m, 2H), 2.52 – 2.40 (m, 2H), 2.26 (br m, 2H), 2.08 (br m, 2H), 1.85 (br m, J = 4.3 Hz, 3H), 1.56 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -68.72 (s); LCMS $(M+H)^+$: 581.3.

Example 126. {cis-3-(4-{[4-(1-hydroxy-1-methylethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (single isomer isolated)



The title compound was prepared as described in Example 125, Step C, using Peak 2 from the chiral HPLC run in that step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.82 (s, 1H), 8.34 (s, 1H), 8.28 (s, 1H), 7.36 (d, J = 3.6 Hz, 1H), 7.33 (d, J = 1.3 Hz, 1H), 6.97 (s, 1H), 6.77 (d, J = 3.6 Hz, 1H), 5.15 (ddd, J = 11.4, 7.6, 3.3 Hz, 1H), 3.14 (s, 2H), 2.92 (tt, J = 7.5, 7.5 Hz, 1H), 2.84 – 2.58 (m, 6H), 2.30 (br m, 2H), 2.13 – 1.99 (m, 2H), 1.94 – 1.74 (m, 2H), 1.56 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -68.72 (s); LCMS $(M+H)^+$: 581.3.

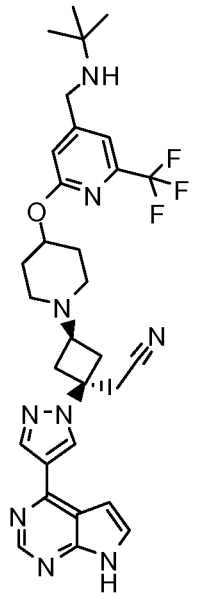
Example 127. {trans-3-(4-{[4-[(tert-butylamino)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



N,N-Diisopropylethylamine (7.6 μL, 0.044 mmol) and methanesulphonic anhydride (5.4 mg, 0.031 mmol, Aldrich) were added to a solution of {trans-3-(4-{[4-(hydroxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (15 mg, 0.022 mmol, Peak 1 from Example 123, Step E) in methylene chloride (0.30 mL). After stirring for one hour, solvent was removed *in vacuo* and tetrahydrofuran (0.20 mL) and tert-butylamine (34 μL, 0.33 mmol, Aldrich) were added. The mixture was sealed in a vial and heated to 50 °C for 2 hours. Solvent and

excess amine were removed *in vacuo*. The residue was stirred in a 1:1 mixture of TFA/DCM for one hour, the solvents were evaporated, and the residue was stirred in Methanol (1 mL) containing ethylenediamine (0.1 mL) until deprotection was complete. Purification via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH), followed by lyophilization afforded product as the free base (5.5 mg, 41%). ^{1}H NMR (300 MHz, dmso) δ 12.12 (s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.43 (s, 1H), 7.08 (d, J = 3.6 Hz, 1H), 7.06 (s, 1H), 5.04 – 4.94 (m, 1H), 3.71 (d, J = 6.4 Hz, 2H), 3.42 (s, 2H), 3.08 – 2.96 (m, 2H), 2.81 (tt, J = 7.6, 7.7 Hz, 1H), 2.63 (br m, 2H), 2.40 – 2.28 (m, 2H), 2.20 – 1.90 (m, 4H), 1.68 (d, J = 10.4 Hz, 2H), 1.05 (s, 9H); ^{19}F NMR (282 MHz, dmso) δ -67.26 (s); LCMS $(M+H)^+$: 608.4.

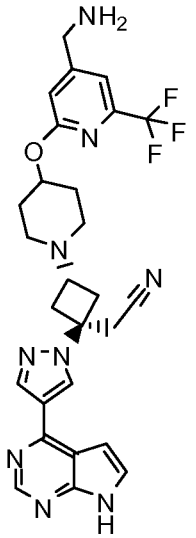
Example 128. **{cis-3-(4-{[4-[(tert-butylamino)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile**



The title compound was prepared according to the procedure of Example 127, using{cis-3-(4-{[4-(hydroxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (15 mg, 0.022 mmol, Peak 2 from Example 123,

Step E) to afford the product as the free base (6.3 mg, 47%). ^{1}H NMR (300 MHz, dmso) δ 12.12 (br s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.40 – 8.38 (m, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.43 (s, 1H), 7.09 – 7.00 (m, 2H), 5.05 – 4.93 (m, 1H), 3.71 (d, J = 6.6 Hz, 2H), 3.47 (s, 2H), 2.93 (tt, J = 7.4, 7.7 Hz, 1H), 2.70 – 2.55 (m, 4H), 2.25 – 1.89 (m, 6H), 1.77 – 1.52 (m, 2H), 1.05 (s, 9H); ^{19}F NMR (282 MHz, dmso) δ -67.25 (s); LCMS $(M+H)^+$: 608.4.

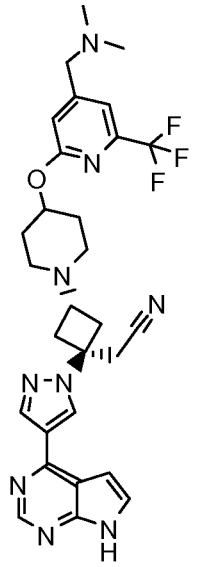
Example 129. {trans-3-(4-{[4-(aminomethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



The title compound was prepared according to the method of Example 127, using 7.0 M Ammonia in methanol (0.16 mL, 1.1 mmol, Aldrich) at room temperature overnight (7.7 mg, 64%). ^{1}H NMR (400 MHz, dmso) δ 12.13 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.43 (s, 1H), 7.08 (d, J = 3.6 Hz, 1H), 7.04 (s, 1H), 5.06 – 4.92 (m, 1H), 3.74 (s, 2H), 3.42 (s, 2H), 3.07 – 2.93 (m, 2H), 2.81 (tt, J = 7.2, 7.4 Hz, 1H), 2.65 (br m, J = 14.0 Hz, 2H), 2.40 – 2.29 (m, 2H), 2.16 (br m, 2H), 2.01 (br m, 2H), 1.77 – 1.52 (m, 2H); ^{19}F NMR (376 MHz, dmso) δ -67.26 (s); LCMS $(M+H)^+$: 551.8.

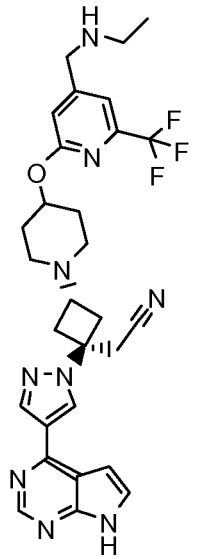
Example 130. {trans-3-(4-{[4-[(dimethylamino)methyl]-6-(trifluoromethyl)pyridin-2-

yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



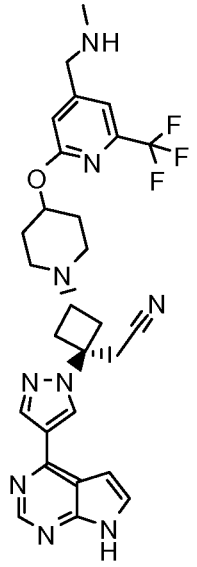
The title compound was prepared according to the method of Example 127, using 2.0 M Dimethylamine in THF (0.11 mL, 0.22 mmol, Aldrich) at room temperature for 2 hours (8.3 mg, 65%). ^{1}H NMR (400 MHz, dmso) δ 12.13 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.36 (s, 1H), 7.08 (d, J = 3.6 Hz, 1H), 6.99 (s, 1H), 5.04 – 4.96 (m, 1H), 3.46 (s, 2H), 3.42 (s, 2H), 3.06 – 2.94 (m, 2H), 2.81 (tt, J = 7.3, 7.4 Hz, 1H), 2.65 (br m, 2H), 2.42 – 2.21 (m, 2H), 2.22 – 2.07 (m, 8H), 2.00 (br m, J = 8.4 Hz, 2H), 1.75 – 1.63 (m, 2H); ^{19}F NMR (376 MHz, dmso) δ -67.35 (s); LCMS $(M+H)^+$: 580.3.

Example 131. {trans-3-(4-{[4-[(ethylamino)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



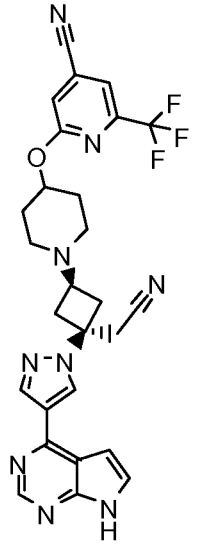
The title compound was prepared according to the procedure of Example 127, using Ethylamine (0.124 mL, 2.20 mmol, Aldrich) at room temperature overnight (6.2 mg, 49%). ^{1}H NMR (400 MHz, dmso) δ 12.13 (s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.41 (s, 1H), 7.08 (d, J = 3.6 Hz, 1H), 7.03 (s, 1H), 4.99 (tt, J = 8.0, 3.2 Hz, 1H), 3.73 (s, 2H), 3.42 (s, 2H), 3.08 – 2.95 (m, 2H), 2.81 (tt, J = 7.4, 7.5 Hz, 1H), 2.65 (br m, J = 12.8 Hz, 2H), 2.48 (q, J = 7.1 Hz, 2H), 2.40 – 2.31 (m, 2H), 2.17 (br m, J = 10.7 Hz, 2H), 2.00 (br m, 2H), 1.77 – 1.55 (m, 2H), 1.01 (t, J = 7.1 Hz, 3H); ^{19}F NMR (376 MHz, dmso) δ -67.29 (s); LCMS (M+H)$^+$: 580.3.

Example 132. {trans-3-(4-{[4-[(methylamino)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



The title compound was prepared according to the procedure of Example 127, using 33 wt% methylamine in ethanol (69 mg, 0.73 mmol) at room temperature overnight (4.7 mg, 57%). ^{1}H NMR (300 MHz, dmso) δ 12.13 (s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.41 (s, 1H), 7.08 (d, J = 3.6 Hz, 1H), 7.02 (s, 1H), 5.05 – 4.95 (m, 1H), 3.68 (s, 2H), 3.42 (s, 2H), 3.07 – 2.95 (m, 2H), 2.81 (tt, J = 7.3, 7.5 Hz, 1H), 2.64 (br m, 2H), 2.41 – 2.30 (m, 2H), 2.23 (s, 3H), 2.21 – 2.09 (m, 2H), 2.01 (br m, 3H), 1.80 – 1.54 (m, 2H); ^{19}F NMR (282 MHz, dmso) δ -67.30 (s); LCMS $(M+H)^+$: 566.3.

Example 133. 2-[(1-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperidin-4-yl)oxy]-6-(trifluoromethyl)isonicotinonitrile (single isomer)



Step A. 2-Chloro-6-(trifluoromethyl)isonicotinonitrile

2-Chloro-4-iodo-6-(trifluoromethyl)pyridine (0.50 g, 1.5 mmol, prepared according to the method described in *European Journal of Organic Chemistry*, (18) 3793-3798; 2004) and copper cyanide (0.52 g, 5.8 mmol) were mixed in N-methylpyrrolidinone (2 mL). The reaction vial was sealed and heated in the microwave to 120 °C for 10 minutes. The mixture was diluted with water and EtOAc and was filtered. The organic layer was washed with water (3x), followed by brine, dried over sodium sulfate and concentrated. Flash chromatography on silica gel, eluting with a gradient from 0-15% EtOAc in hexanes afforded product as a colorless oil (0.24 g, 64%).

Step B. tert-Butyl 4-{[4-(aminocarbonyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidine-1-carboxylate

Tert-butyl 4-hydroxypiperidine-1-carboxylate (0.37 g, 1.8 mmol, Aldrich) was added to sodium hydride (74 mg, 1.8 mmol, 60% in mineral oil) in tetrahydrofuran (2.1 mL). After stirring for 45 minutes, 2-chloro-6-(trifluoromethyl)isonicotinonitrile (0.24 g, 0.93 mmol, from Step A) in tetrahydrofuran (1.3 mL) was introduced. After stirring overnight, the mixture was diluted with water and extracted with EtOAc. The combined extracts were washed with water, brine, dried over sodium sulfate, filtered and concentrated. Flash chromatography, eluting with a gradient from 0-40% EtOAc in hexanes afforded product (0.20 g, 44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 1.2

Hz, 1H), 7.23 (dd, J = 1.3, 0.6 Hz, 1H), 6.15 (s, 1H), 5.75 (s, 1H), 5.30 (tt, J = 7.7, 3.8 Hz, 1H), 3.95 – 3.62 (m, 4H), 3.33 (ddd, J = 13.5, 8.4, 3.7 Hz, 2H), 3.02 (ddd, J = 13.3, 9.8, 3.4 Hz, 2H), 1.58 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -68.97 (s); LCMS $(M+Na)^+$: 412.0.

Step C. 2-(Piperidin-4-yloxy)-6-(trifluoromethyl)isonicotinamide

tert-Butyl 4-{[4-(aminocarbonyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidine-1-carboxylate (0.20 g, 0.41 mmol, from Step B) was dissolved in 1,4-dioxane (3.0 mL, 38 mmol) and treated with 4.0 M hydrogen chloride in dioxane (2.4 mL, 9.8 mmol). After 2.5 hours, the mixture was treated with ammonium hydroxide to achieve pH 11, and 15 mL of acetonitrile was added. The mixture was filtered and purified via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) to afford product (72 mg, 60%). ^{1}H NMR (400 MHz, dmso) δ 8.35 (s, 1H), 7.91 (s, 1H), 7.76 (d, J = 1.2 Hz, 1H), 7.49 (s, 1H), 5.05 (tt, J = 8.9, 4.1 Hz, 1H), 2.95 (dt, J = 12.6, 4.2 Hz, 2H), 2.57 (ddd, J = 12.7, 10.0, 2.9 Hz, 2H), 2.01 – 1.87 (m, 2H), 1.60 – 1.41 (m, 2H); ^{19}F NMR (376 MHz, dmso) δ -67.49 (s); LCMS $(M+H)^+$: 290.1.

Step D. 2-[(1-{cis-3-(Cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperidin-4-yl)oxy]-6-(trifluoromethyl)isonicotinamide and 2-[(1-{trans-3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperidin-4-yl)oxy]-6-(trifluoromethyl)isonicotinamide (each diastereomer isolated)

Sodium cyanoborohydride (21 mg, 0.34 mmol) and zinc dichloride (23 mg, 0.17 mmol) were combined in methanol (1.2 mL) and stirred for 2 hours. Separately, {3-oxo-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.11 g, 0.27 mmol, from Step 7 of Example 1a) and 2-(piperidin-4-yloxy)-6-(trifluoromethyl)isonicotinamide (70. mg, 0.24 mmol, from Step C) were stirred in methanol (3.4 mL) to dissolve, then the solution combining $ZnCl_2$ and $NaCNBH_3$ was added. After stirring overnight, the mixture was purified via preparative

HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) to afford two isomers: Peak 1 (1st peak eluted) was the cis- isomer (49 mg, 29%); Peak2 (second peak to elute) was the trans- isomer (56 mg, 33%).

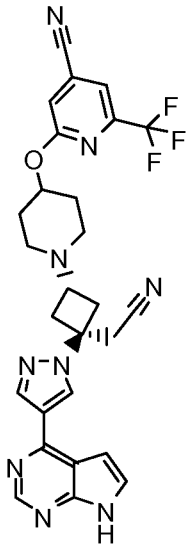
Peak 1, Cis-: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.45 (s, 1H), 8.36 (s, 1H), 7.63 (d, J = 1.2 Hz, 1H), 7.46 (d, J = 3.7 Hz, 1H), 7.28 (s, 1H), 6.86 (d, J = 3.7 Hz, 1H), 6.17 (s, 1H), 5.80 (s, 1H), 5.73 (s, 2H), 5.29 – 5.19 (m, 1H), 3.72 – 3.44 (m, 2H), 3.21 (s, 2H), 3.06 – 2.49 (m, 7H), 2.48 – 2.22 (m, 2H), 2.24 – 2.01 (m, 2H), 1.99 – 1.80 (m, 2H), 1.08 – 0.87 (m, 2H), 0.00 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -68.97 (s); LCMS $(M+H)^+$: 696.1. Peak 2, Trans-: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.48 (s, 1H), 8.33 (s, 1H), 7.57 (d, J = 1.2 Hz, 1H), 7.41 (d, J = 3.7 Hz, 1H), 7.22 (s, 1H), 6.82 (d, J = 3.7 Hz, 1H), 6.12 (s, 1H), 5.74 (s, 1H), 5.68 (s, 2H), 5.19 (tt, J = 7.5, 3.9 Hz, 1H), 3.62 – 3.46 (m, 2H), 3.22 (s, 2H), 3.11 – 2.99 (m, 2H), 2.93 (tt, J = 6.4, 7.0 Hz, 1H), 2.66 (br m, 2H), 2.57 – 2.41 (m, 2H), 2.27 (br m, 2H), 2.05 (br m, 2H), 1.93 – 1.76 (m, 2H), 1.01 – 0.77 (m, 2H), -0.06 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -68.97 (s); LCMS $(M+H)^+$: 696.1.

Step E. 2-[(1-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperidin-4-yl)oxy]-6-(trifluoromethyl)isonicotinonitrile

Triethylamine (16 μL, 0.11 mmol) followed by trichloroacetic anhydride (16 μL, 0.086 mmol, Aldrich) was added to a solution of 2-[(1-{cis-3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperidin-4-yl)oxy]-6-(trifluoromethyl)isonicotinamide (20. mg, 0.029 mmol, Peak 1 from Step D) in methylene chloride (1.5 mL) at 0 °C. After 25 minutes, 1.5 mL TFA was added to the reaction. After stirring for one hour, TFA and DCM removed *in vacuo*. The residue was dissolved in 1.0 mL methanol, and 0.20 mL ethylenediamine was added. After deprotection was complete, preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) was used to afford product as the free base (13 mg, 83%). ^{1}H NMR (400 MHz, dmso) δ 12.13 (s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.39 (s, 1H), 8.00 (s, 1H), 7.78 (s, 1H), 7.60 (d, J = 3.5 Hz, 1H), 7.06 (d, J = 3.5 Hz, 1H), 5.04 (tt, J = 7.5, 3.2 Hz, 1H), 3.47 (s, 2H), 2.94 (tt, J = 7.6, 7.7 Hz, 1H), 2.75 – 2.55 (m, 6H), 2.19 (br m, J = 10.5 Hz, 2H), 2.01 (br m, 2H), 1.78 – 1.58 (m, 2H); ^{19}F NMR

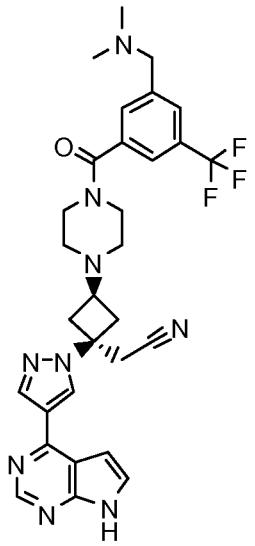
(376 MHz, dmso) δ -67.77 (s); LCMS $(M+H)^+$: 548.0.

Example 134. 2-[(1-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperidin-4-yl)oxy]-6-(trifluoromethyl)isonicotinonitrile (single isomer prepared)



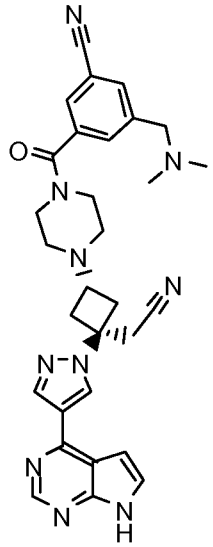
The title compound was prepared according to the procedure of Example 133, Step E, using 2-[(1-{trans-3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperidin-4-yl)oxy]-6-(trifluoromethyl)isonicotinamide (48 mg, 0.069 mmol, Peak 2 from Example 133, Step D) to afford product as the free base (29 mg, 77%). ^{1}H NMR (400 MHz, dmso) δ 12.13 (s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (d, J = 0.6 Hz, 1H), 8.00 (d, J = 1.0 Hz, 1H), 7.77 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.08 (d, J = 3.6 Hz, 1H), 5.09 – 4.94 (m, 1H), 3.42 (s, 2H), 3.08 – 2.96 (m, 2H), 2.82 (tt, J = 7.4, 7.4 Hz, 1H), 2.66 (br m, J = 12.3 Hz, 2H), 2.41 – 2.28 (m, 2H), 2.15 (br m, J = 10.8 Hz, 2H), 2.03 (br m, 2H), 1.81 – 1.52 (m, 2H); ^{19}F NMR (376 MHz, dmso) δ -67.78 (s); LCMS $(M+H)^+$: 548.0.

Example 135. {cis-3-{4-[3-[(dimethylamino)methyl]-5-(trifluoromethyl)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Lithium 3-[(dimethylamino)methyl]-5-(trifluoromethyl)benzoate (23.1 mg, 0.0913 mmol, US 2010/197924) was dissolved in tetrahydrofuran (0.67 mL), triethylamine (33.9 μL, 0.244 mmol) and N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (32.4 mg, 0.0852 mmol) were added, the mixture was stirred for 15 minutes. {cis-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (30.0 mg, 0.0609 mmol, from Step 9 of Example 1a) was then added , and the reaction was stirred for two hours. Ethyl acetate and water were added and the layers were separated. The organic layer was washed with water, 0.1N NaOH and sat. NaCl, dried over sodium sulfate, and concentrated. The residue was dissolved in a 1:1 mixture of DCM:TFA, stirred for 1 hour, and concentrated again. Methanol (1 mL) was added, followed by 0.2 mL of ethylenediamine. The reaction was stirred until deprotection was complete. Purification via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) followed by lyophilization afforded product as the free base (20 mg, 40%). ^1H NMR (400 MHz, dmso) δ 12.14 (br s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.40 (s, 1H), 7.71 (br m, 1H), 7.62 (br m, 1H), 7.61 (d, J = 3.6 Hz, 1H), 7.59 (br m, 1H), 7.06 (d, J = 3.6 Hz, 1H), 3.64 (br m, 2H), 3.51 (s, 2H), 3.47 (s, 2H), 3.30 (br m, 2H), 2.95 (tt, J = 7.6, 7.7 Hz, 1H), 2.69 – 2.54 (m, 4H), 2.40 (br m, 2H), 2.29 (br m, 2H), 2.15 (s, 6H); ^{19}F NMR (376 MHz, dmso) δ -61.46 (s); LCMS $(M+H)^+$: 592.3.

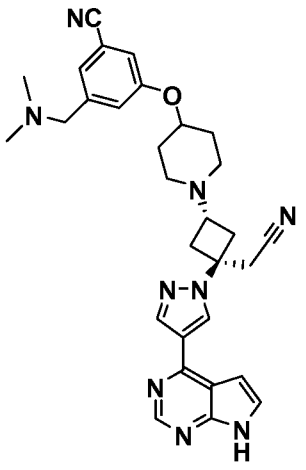
Example 136. 3-[(4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)carbonyl]-5-[(dimethylamino)methyl]benzonitrile



Methyl 3-bromo-5-[(dimethylamino)methyl]benzoate (0.30 g, 1.1 mmol, from Example 43, Step A) was hydrolyzed by stirring with lithium hydroxide monohydrate (0.555 g, 13.2 mmol) in a mixture of THF (20 mL) and water (6 mL) for 3 hours. The mixture was acidified by the addition of 1 N HCl to achieve pH 10, and the solvents were removed *in vacuo*. Purification by preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) to afford 0.26 g of product (91%). A portion of the 3-bromo-5-[(dimethylamino)methyl]benzoic acid (31.4 mg, 0.122 mmol) obtained by hydrolysis was dissolved in tetrahydrofuran (0.90 mL), and triethylamine (45.3 μL, 0.325 mmol) and N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (43.2 mg, 0.114 mmol) were added. The mixture was stirred for 15 minutes, then {trans-3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (40.0 mg, 0.0812 mmol, from Step 1 of Example 1b) was added. The reaction was stirred for two hours and the reaction mixture was partitioned between ethyl acetate and water. The layers were separated and the organic layer was washed with water, 0.1 N NaOH and sat. NaCl, dried over sodium sulfate and concentrated. The residue was dissolved in N,N-

dimethylformamide (1.0 mL) and zinc cyanide (57 mg, 0.49 mmol) was added. The reaction mixture was degassed by bubbling a stream of nitrogen through the mixture for 10 minutes. Tetrakis(triphenylphosphine)palladium(0) (19 mg, 0.016 mmol) was then added. The reaction was heated to 120 °C in the microwave for 30 minutes. The reaction mixture was partitioned between water and ethyl acetate. After separation of layers, the organic layer was washed twice with water, once with brine, dried over sodium sulfate and concentrated. The residue was stirred in a 1:1 mixture of DCM:TFA for one hour, then concentrated. To complete the deprotection, the residue was redissolved in methanol (1 mL) and 0.2 mL of ethylenediamine was added and stirred until deprotection was complete. Purification via two successive preparative HPLC-MS runs (C18 eluting first with acidic method, using a gradient of MeCN/H_2O containing 0.1% TFA, then via basic method: C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) followed by lyophilization, afforded the product as the free base (14.1 mg, 31%). ^{1}H NMR (400 MHz, dmso) δ 12.13 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.80 (dd, 1H), 7.77 (dd, 1H), 7.62 (dd, 1H), 7.60 (d, *J* = 3.6 Hz, 1H), 7.07 (d, *J* = 3.6 Hz, 1H), 3.65 (br m, 2H), 3.46 (s, 2H), 3.43 (s, 2H), 3.31 (br m, 2H), 3.07 – 2.93 (m, 2H), 2.83 (tt, *J* = 7.2, 7.3 Hz, 1H), 2.44 – 2.21 (m, 6H), 2.14 (s, 6H); LCMS $(M+H)^+$: 549.2.

Example 137. 3-[(1-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperidin-4-yl)oxy]-5-[(dimethylamino)methyl]benzonitrile



Step 1. tert-Butyl 4-[3-bromo-5-(methoxycarbonyl)phenoxy]piperidine-1-carboxylate

The title compound was prepared according to the method of Example 40, Step 5 using methyl 3-bromo-5-hydroxybenzoate as starting material. LCMS $(M+H-100)^+$: 314.0, 316.0.

Step 2. tert-Butyl 4-[3-bromo-5-(hydroxymethyl)phenoxy]piperidine-1-carboxylate

To a solution of tert-butyl 4-[3-bromo-5-(methoxycarbonyl)phenoxy]piperidine-1-carboxylate (520 mg, 1.2 mmol) in THF (10 mL) was added lithium tetrahydroborate (27.3 mg, 1.26 mmol). The resulting solution was stirred at room temperature for 1 hour. The reaction was quenched with 1 N HCl. The organic solution was washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash chromatography on a silica gel column to give the desired product. LCMS $(M+Na)^+$: 408.1, 410.1.

Step 3. tert-Butyl 4-(3-bromo-5-formylphenoxy)piperidine-1-carboxylate

To a solution of tert-butyl 4-[3-bromo-5-(hydroxymethyl)phenoxy]piperidine-1-carboxylate (0.47 g, 1.2 mmol) in DCM (20 mL) at 0 °C was added Dess-Martin periodinane (0.67 g, 1.6 mmol). After stirring for 2 hours, the reaction solution was poured into saturated $NaHCO_3$, and extracted with DCM (3x). The combined extracts were washed with brine.The organic layer was dried over sodium sulfate, decanted and evaporated to give the desired product that was used without further purification.

Step 4. tert-Butyl 4-{3-bromo-5-[(E)-(hydroxyimino)methyl]phenoxy}piperidine-1-carboxylate

To the solution of tert-butyl 4-(3-bromo-5-formylphenoxy)piperidine-1-carboxylate (205 mg, 0.533 mmol) in ethanol (1.9 mL) and water (0.6 mL), hydroxylamine hydrochloride (40.8 mg, 0.587 mmol) and sodium acetate (61.3 mg, 0.747 mmol) were added sequentially, then the resulting solution was refluxed for 1 hour. The most organic solvent was removed *in vacuo* and the solution was diluted with water. The resultant precipitate was collected and dried under vacuum to give the desired product as

white solid. LCMS $(M+H)^+$: 399.1, 401.1.

Step 5. tert-Butyl 4-(3-bromo-5-cyanophenoxy)piperidine-1-carboxylate

To a solution of tert-butyl 4-{3-bromo-5-[(E)-(hydroxyimino)methyl]phenoxy}piperidine-1-carboxylate (157 mg, 0.393 mmol) in pyridine (1.2 mL) was added methanesulfonyl chloride (0.12 mL, 1.6 mmol). The reaction mixture was heated at 60 °C for 2 hours. The reaction solution was diluted with ethyl acetate and saturated $CuSO_4$ solution. The organic layer was washed with $CuSO_4$ twice, 1 N HCl, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column to give the desired product as white solid. LCMS $(M+H)^+$: 381.1, 383.1.

Step 6. tert-Butyl 4-{3-cyano-5-[(dimethylamino)methyl]phenoxy}piperidine-1-carboxylate

This compound was prepared according to the method of Example 40, Step 6 using *tert*-butyl 4-(3-bromo-5-cyanophenoxy)piperidine-1-carboxylate as starting material. LCMS $(M+H)^+$: 360.1.

Step 7. 3-[(Dimethylamino)methyl]-5-(piperidin-4-yloxy)benzonitrile

This compound was prepared according to the method of Example 40, Step 7 using *tert*-butyl 4-{3-cyano-5-[(dimethylamino)methyl]phenoxy}piperidine-1-carboxylate as starting material. LCMS $(M+H)^+$: 260.1.

Step 8. 3-[(1-{trans-3-(Cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperidin-4-yl)oxy]-5-[(dimethylamino)methyl]benzonitrile, 3-[(1-{trans-3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperidin-4-yl)oxy]-5-[(dimethylamino)methyl]benzonitrile

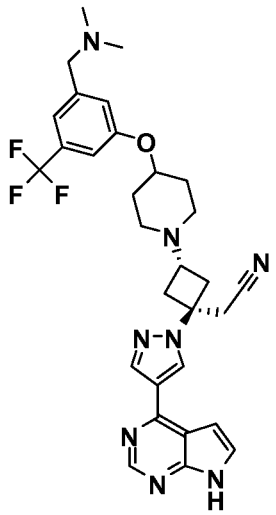
These compounds were prepared according to the method of Example 40, Step 8 using 3-[(dimethylamino)methyl]-5-(piperidin-4-yloxy)benzonitrile as starting material.

LCMS $(M+H)^+$: 666.3

Step 9. 3-[(1-{trans-3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperidin-4-yl)oxy]-5-[(dimethylamino)methyl]benzonitrile

The title compounds were prepared according to the method of Example 40, Step 9 using 3-[(1-{trans-3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperidin-4-yl)oxy]-5-[(dimethylamino)methyl]benzonitrile as starting materials. LCMS $(M+H)^+$: 536.3.

Example 138. {trans-3-{4-[3-[(dimethylamino)methyl]-5-(trifluoromethyl)phenoxy]piperidin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step 1. Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)benzoate

The mixture of methyl 3-bromo-5-(trifluoromethyl)benzoate (6.72g, 23.7 mmol), 4,4,5,5,4',4',5'5'-octamethy-[2,2']bi[1,3,2]dioxaborolayl] (6.63, 26.1 mmol), Pd (dppf) (0.58 g, 0.71 mmol), and potassium acetate (7.0 g, 71 mmol) in dioxane (50 mL) was degassed with N_2 and heated at 100 °C for 14 hours. The reaction mixture was cooled to room temperature. The reaction mixture was filtered through a pad of celite and washed

with EtOAc. The filtrates were concentrated and the crude residue was purified by flash chromatography on a silica gel column to give the desired product. (7.2 g , 92%). LCMS $(M+H)^+$: 331.1.

Step 2. 3-Hydroxy-5-(trifluoromethyl)benzoic acid

A mixture of copper(II) sulfate pentahydrate (0.43 g, 1.7 mmol), *o*-phenanthroline (0.62 g, 3.4 mmol), methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)benzoate (5.70 g, 17.3 mmol), and potassium hydroxide (3.42 g, 51.8 mmol) in water (90 mL) was stirred at room temperature open to air overnight. The reaction was acidified with 6 M HCl and diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate once. The combined organic solutions were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude was used in the next step without purification.

Step 3. Methyl 3-hydroxy-5-(trifluoromethyl)benzoate

To a solution of 3-hydroxy-5-(trifluoromethyl)benzoic acid (3.56 g, 17.3 mmol) in methanol (110 mL) was added 4.0 M hydrogen chloride in dioxane (110 mL, 460 mmol). The resulting mixture was stirred at room temperature overnight. The solvent was concentrated. The residue was purified by flash chromatography on a silica gel column to give the desired product as white solid.

Step 4. tert-Butyl 4-[3-(methoxycarbonyl)-5-(trifluoromethyl)phenoxy]piperidine-1-carboxylate

The title compound was prepared according to the method of Example 40, Step 5 using methyl 3-hydroxy-5-(trifluoromethyl)benzoate as starting material. LCMS $(M+H-100)^+$: 304.0.

Step 5. tert-Butyl 4-[3-(hydroxymethyl)-5-(trifluoromethyl)phenoxy]piperidine-1-carboxylate

The title compound was prepared according to the method of Example 137, Step 2

(this is a $LiBH_4$ reduction) using *tert*-butyl 4-[3-(methoxycarbonyl)-5-(trifluoromethyl)phenoxy]piperidine-1-carboxylate as starting material. LCMS $(M+H-56)^+$: 320.0.

Step 6. tert-Butyl 4-[3-formyl-5-(trifluoromethyl)phenoxy]piperidine-1-carboxylate

The title compound was prepared according to the method of Example 137, Step 3 using *tert*-butyl 4-[3-(methoxycarbonyl)-5-(trifluoromethyl)phenoxy]piperidine-1-carboxylate as starting material. LCMS $(M+H-56)^+$: 318.0.

Step 7. tert-Butyl 4-[3-[(dimethylamino)methyl]-5-(trifluoromethyl)phenoxy]piperidine-1-carboxylate

The title compound was prepared according to the method of Example 41, Step 2 using *tert*-butyl 4-[3-formyl-5-(trifluoromethyl)phenoxy]piperidine-1-carboxylate and dimethylamine as starting materials. LCMS $(M+H)^+$: 403.2.

Step 8. N,N-Dimethyl-1-[3-(piperidin-4-yloxy)-5-(trifluoromethyl)phenyl]methanamine

This compound was prepared according to the method of Example 40, Step 7 using *tert*-butyl 4-[3-[(dimethylamino)methyl]-5-(trifluoromethyl)phenoxy]piperidine-1-carboxylate as starting material. LCMS $(M+H)^+$: 303.1.

Step 9. {trans-3-{4-[3-[(dimethylamino)methyl]-5-(trifluoromethyl)phenoxy]piperidin-1-yl}-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

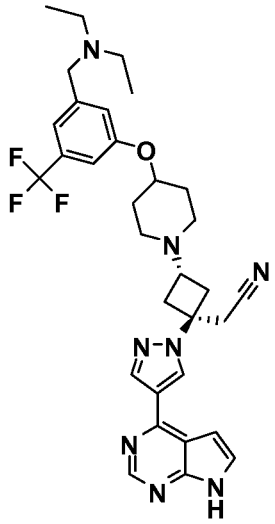
This compound was prepared according to the method of Example 40, Step 8 using *N,N*-dimethyl-1-[3-(piperidin-4-yloxy)-5-(trifluoromethyl)phenyl]methanamine as starting material. LCMS $(M+H)^+$: 709.3.

Step 10. {trans-3-{4-[3-[(Dimethylamino)methyl]-5-(trifluoromethyl)phenoxy]piperidin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

The title compound was prepared according to the method of Example 40, Step 9

using {trans-3-{4-[3-[(dimethylamino)methyl]-5-(trifluoromethyl)phenoxy]piperidin-1-yl}-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile as starting materials. LCMS $(M+H)^+$: 579.2.

Example 139. {trans-3-{4-[3-[(diethylamino)methyl]-5-(trifluoromethyl)phenoxy]piperidin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step 1. tert-Butyl 4-[3-[(diethylamino)methyl]-5-(trifluoromethyl)phenoxy]piperidine-1-carboxylate trifluoroacetate

The title compound was prepared according to the method of Example 41, Step 2 using *tert*-butyl 4-[3-formyl-5-(trifluoromethyl)phenoxy]piperidine-1-carboxylate and diethylamine as starting materials. LCMS $(M+H-100)^+$: 331.2.

Step 2. N N-Ethyl-N-[3-(piperidin-4-yloxy)-5-(trifluoromethyl)benzyl]ethanamine

This compound was prepared according to the method of Example 40, Step 7 using *tert*-butyl 4-[3-[(diethylamino)methyl]-5-(trifluoromethyl)phenoxy]piperidine-1-carboxylate trifluoroacetate as starting material. LCMS $(M+H)^+$: 331.2.

Step 3. {cis-3-{4-[3-[(Diethylamino)methyl]-5-(trifluoromethyl)phenoxy]piperidin-1-yl}-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-

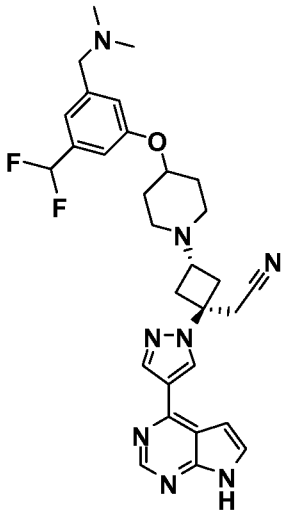
1-yl]cyclobutyl}acetonitrile, {trans-3-{4-[3-[(diethylamino)methyl]-5-(trifluoromethyl)phenoxy]piperidin-1-yl}-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

These compounds were prepared according to the method of Example 40, Step 8 using *N,N*-ethyl-N-[3-(piperidin-4-yloxy)-5-(trifluoromethyl)benzyl]ethanamine as starting material. LCMS $(M+H)^+$: 737.3

Step 4. {trans-3-{4-[3-[(diethylamino)methyl]-5-(trifluoromethyl)phenoxy]piperidin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

The title compound was prepared according to the method of Example 40, Step 9 using {trans-3-{4-[3-[(diethylamino)methyl]-5-(trifluoromethyl)phenoxy]piperidin-1-yl}-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile as starting materials. LCMS $(M+H)^+$: 607.3.

Example 140. {trans-3-(4-{3-(difluoromethyl)-5-[(dimethylamino)methyl]phenoxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step 1. tert-Butyl 4-{3-(difluoromethyl)-5-[(dimethylamino)methyl]phenoxy}piperidine-1-carboxylate

This compound was prepared according to the method of Example 40, Step 6

using *tert*-butyl 4-[3-bromo-5-(difluoromethyl)phenoxy]piperidine-1-carboxylate as starting material. LCMS $(M+H-100)^+$: 331.2.

Step 2. 1-[3-(Difluoromethyl)-5-(piperidin-4-yloxy)phenyl]-N,N-dimethylmethanamine

This compound was prepared according to the method of Example 40, Step 7 using *tert*-butyl 4-{3-(difluoromethyl)-5-[(dimethylamino)methyl]phenoxy}piperidine-1-carboxylate as starting material. LCMS $(M+H)^+$: 331.2.

Step 3. {cis-3-(4-{3-(Difluoromethyl)-5-[(dimethylamino)methyl]phenoxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile, {trans-3-(4-{3-(difluoromethyl)-5-[(dimethylamino)methyl]phenoxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

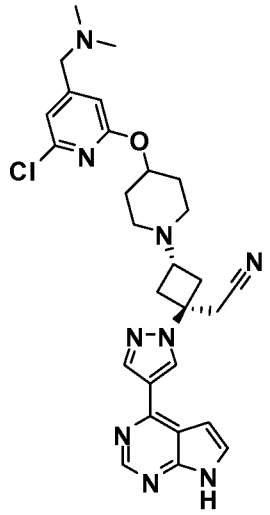
These compounds were prepared according to the method of Example 40, Step 8 using 1-[3-(difluoromethyl)-5-(piperidin-4-yloxy)phenyl]-N,N-dimethylmethanamine as starting material. LCMS $(M+H)^+$: 691.3.

Step 4. {trans-3-(4-{3-(Difluoromethyl)-5-[(dimethylamino)methyl]phenoxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

The title compound was prepared according to the method of Example 40, Step 9 using {trans-3-(4-{3-(difluoromethyl)-5-[(dimethylamino)methyl]phenoxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile as starting materials. ^{1}H NMR (300 MHz, DMSO): δ 12.06 (brs, 1H), 8.77 (s, 1H), 8.63 (s, 1H), 8.36 (s, 1H), 7.54 (d, 1H), 6.94 (m, 5H), 4.40 (m, 1H), 3.31 (m, 4H), 3.95 (m, 2H), 2.73 (m, 2H), 2.55 (m, 2H), 2.27 (m, 2H), 2.05 (m, 8H), 1.91 (m, 2H), 1.59 (m, 2H) ; ; LCMS $(M+H)^+$: 561.3.

Example 141. {trans-3-[4-({6-chloro-4-[(dimethylamino)methyl]pyridin-2-yl}oxy)piperidin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-

yl]cyclobutyl}acetonitrile



Step 1. tert-Butyl 4-({6-chloro-4-[(dimethylamino)methyl]pyridin-2-yl}oxy)piperidine-1-carboxylate

To a solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (44.2 mg, 0.219 mmol) in DMF (0.7 mL) was added sodium hydride (13.2 mg, 0.329 mmol). After stirring for 30 minutes, 1-(2,6-dichloropyridin-4-yl)-*N,N*-dimethylmethanamine (45 mg, 0.22 mmol) was added to the reaction vial. The reaction solution was heated at 100 °C overnight. The reaction solution was diluted with methanol and purified with preparative LCMS to give the desired product. LCMS $(M+H)^+$: 370.1.

Step 2. 1-[2-Chloro-6-(piperidin-4-yloxy)pyridin-4-yl]-N,N-dimethylmethanamine

This compound was prepared according to the method of Example 40, Step 7 using *tert*-butyl 4-({6-chloro-4-[(dimethylamino)methyl]pyridin-2-yl}oxy)piperidine-1-carboxylate as starting material. LCMS $(M+H)^+$: 270.1.

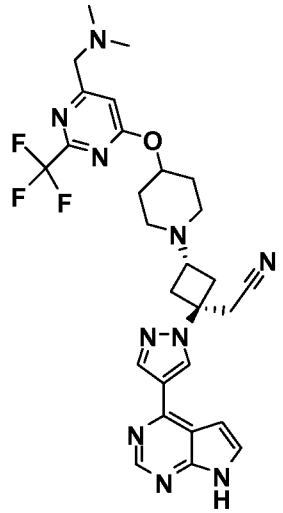
Step 3. {cis-3-[4-({6-Chloro-4-[(dimethylamino)methyl]pyridin-2-yl}oxy)piperidin-1-yl]-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile, {trans-3-[4-({6-chloro-4-[(dimethylamino)methyl]pyridin-2-yl}oxy)piperidin-1-yl]-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

These compounds were prepared according to the method of Example 40, Step 8 using 1-[2-chloro-6-(piperidin-4-yloxy)pyridin-4-yl]-N,N-dimethylmethanamine as starting material. LCMS $(M+H)^+$: 676.3

Step 4. {trans-3-(4-{3-(Difluoromethyl)-5-[(dimethylamino)methyl]phenoxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

The title compound was prepared according to the method of Example 40, Step 9 using {trans-3-[4-({6-chloro-4-[(dimethylamino)methyl]pyridin-2-yl}oxy)piperidin-1-yl]-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile as starting materials. ^{1}H NMR (400 MHz, DMSO): δ ; LCMS $(M+H)^+$: 546.3.

Example 142. {trans-3-(4-{[6-[(dimethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step 1. tert-Butyl 4-{[6-chloro-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate

In a reaction flask, *tert*-butyl 4-hydroxypiperidine-1-carboxylate (2.02 g, 10.0 mmol) and 4,6-dichloro-2-(trifluoromethyl)pyrimidine (2.18 g, 10.0 mmol) were dissolved in THF (19.7 mL) and cooled to 0 °C. Sodium hydride (0.603 g, 15.1 mmol)

was added and then the mixture was stirred for 30 minutes at 0 °C and at 25 °C for another 16 hours. The reaction was quenched with water, and was extracted with ethyl acetate and the organic extracts were washed with water, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give the product.

Step 2. tert-Butyl 4-{[2-(trifluoromethyl)-6-vinylpyrimidin-4-yl]oxy}piperidine-1-carboxylate

To a solution of *tert*-butyl 4-{[6-chloro-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate (0.742 g, 1.94 mmol) in DMF (8.7 mL) was added (2-ethenyl)tri-n-butyltin (0.682 mL, 2.33 mmol) and tetrakis(triphenylphosphine)palladium(0) (112 mg, 0.0972 mmol). The reaction solution was stirred at 65 °C overnight. The reaction solution was diluted with ethyl acetate and saturated KF solution. The aqueous layer was extracted with ethyl acetate three times. The combined organic solutions were dried over Na_2SO_4, filtered and concentrated. The residue was purified with silica gel column to give the desired product as light brown oil. LCMS $(M+H)^+$: 374.2.

Step 3. tert-Butyl 4-{[6-(1,2-dihydroxyethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate

To a solution of *tert*-butyl 4-{[2-(trifluoromethyl)-6-vinylpyrimidin-4-yl]oxy}piperidine-1-carboxylate (614 mg, 1.64 mmol) in methanol (7 mL) and *tert*-butyl alcohol (5.2 mL) was added *N*-methylmorpholine *N*-oxide (212 mg, 1.81 mmol) and water (5.2 mL). To this solution was then added osmium tetraoxide (20.9 mg, 0.0822 mmol). After stirring for 3 hours, another equivalent of *N*-methylmorpholine *N*-oxide was added. The reaction was stirred at room temperature overnight. The solution was concentrated and diluted with water and extracted with ethyl acetate twice, washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash chromatography on a silica gel column to give the desired product. LCMS $(M+H)^+$: 408.2.

Step 4. tert-Butyl 4-{[6-formyl-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate

To a solution of *tert*-butyl 4-{[6-(1,2-dihydroxyethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate (542 mg, 1.33 mmol) in THF (10. mL) and water (6.0 mL) was added acetic acid (20. μL, 0.35 mmol) and sodium periodate (854 mg, 3.99 mmol) at -5 °C. After stirring for 30 minutes, the reaction mixture was diluted with ether and water. The aqueous layer was extracted with ethyl acetate once and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The organic solvent was removed *in vacuo* and the residue was purified with silica gel column to give the desired product as colorless oil. LCMS $(M+H)^+$: 376.1.

Step 5. tert-Butyl 4-{[6-[(dimethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate

The title compound was prepared according to the method of Example 41, Step 2 using *tert*-butyl 4-{[6-formyl-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate and dimethylamine as starting materials. LCMS $(M+H-100)^+$: 405.2.

Step 6. N,N-Dimethyl-1-[6-(piperidin-4-yloxy)-2-(trifluoromethyl)pyrimidin-4-yl]methanamine

This compound was prepared according to the method of Example 40, Step 7 using *tert*-butyl 4-{[6-[(dimethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate as starting material. LCMS $(M+H)^+$: 305.1.

Step 7. {cis-3-(4-{[6-[(Dimethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile, {trans-3-(4-{[6-[(dimethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-

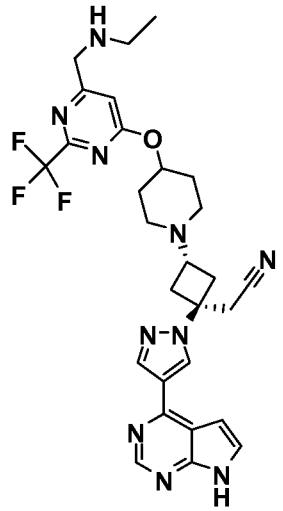
yl]cyclobutyl}acetonitrile

These compounds were prepared according to the method of Example 40, Step 8 using *N,N*-dimethyl-1-[6-(piperidin-4-yloxy)-2-(trifluoromethyl)pyrimidin-4-yl]methanamine as starting material. LCMS $(M+H)^+$: 711.3

Step 8. {trans-3-(4-{[6-[(Dimethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

The title compound was prepared according to the method of Example 40, Step 9 using {trans-3-(4-{[6-[(dimethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile as starting materials. ^{1}H NMR (400 MHz, CD3OD): δ 8.74 (s, 1H), 8.67 (s, 1H), 8.41 (s, 1H), 7.52 (d, 1H), 7.06 (s, 1H), 6.99 (d, 1H), 5.26 (m, 1H), 3.59 (m, 2H), 3.30 (m, 1H), 3.09 (m, 2H), 2.96 (m, 2H), 2.76 (m, 2H), 2.49 (m, 2H), 2.30 (m, 8H), 2.14 (m, 2H), 1.91 (m, 2H); LCMS $(M+H)^+$: 581.3.

Example 143. {trans-3-(4-{[6-[(ethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step 1. tert-Butyl 4-{[6-[(ethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-

yl]oxy}piperidine-1-carboxylate

This compound was prepared according to the method of Example 41, Step 2 using *tert*-butyl 4-{[6-formyl-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate and ethylamine as starting materials. LCMS $(M+H)^+$: 405.2.

Step 2. N-{[6-(Piperidin-4-yloxy)-2-(trifluoromethyl)pyrimidin-4-yl]methyl}ethanamine

This compound was prepared according to the method of Example 40, Step 7 using *tert*-butyl 4-{[6-[(ethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate as starting material. LCMS $(M+H)^+$: 305.2.

Step 3. {cis-3-(4-{[6-[(Ethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile, {trans-3-(4-{[6-[(ethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

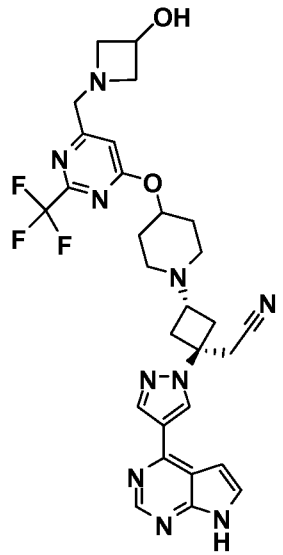
These compounds were prepared according to the method of Example 40, Step 8 using *N*-{[6-(piperidin-4-yloxy)-2-(trifluoromethyl)pyrimidin-4-yl]methyl}ethanamine as starting material. LCMS $(M+H)^+$: 711.3.

Step 4. {trans-3-(4-{[6-[(Ethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

The title compounds were prepared according to the method of Example 40, Step 9 using {trans-3-(4-{[6-[(ethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile as starting materials. LCMS $(M+H)^+$: 581.3.

Example 144. {trans-3-(4-{[6-[(3-hydroxyazetidin-1-yl)methyl]-2-

(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step 1. tert-Butyl 4-{[6-[(3-hydroxyazetidin-1-yl)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate

This compound was prepared according to the method of Example 41, Step 2 using *tert*-butyl 4-{[6-formyl-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate and azetidin-3-ol as starting materials. LCMS $(M+H)^+$: 433.3.

Step 2. 1-{[6-(Piperidin-4-yloxy)-2-(trifluoromethyl)pyrimidin-4-yl]methyl}azetidin-3-ol

This compound was prepared according to the method of Example 40, Step 7 using *tert*-butyl 4-{[6-[(3-hydroxyazetidin-1-yl)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate as starting material. LCMS $(M+H)^+$: 333.1.

Step 3. {cis-3-(4-{[6-[(3-Hydroxyazetidin-1-yl)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile, {trans-3-(4-{[6-[(3-hydroxyazetidin-1-yl)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

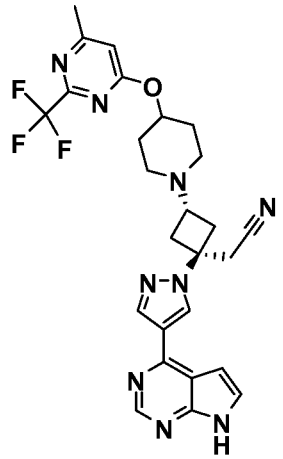
These compounds were prepared according to the method of Example 40, Step 8

using 1-{[6-(piperidin-4-yloxy)-2-(trifluoromethyl)pyrimidin-4-yl]methyl}azetidin-3-ol as starting material. LCMS $(M+H)^+$: 739.3.

Step 4. {trans-3-(4-{[6-[(3-Hydroxyazetidin-1-yl)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

The title compound was prepared according to the method of Example 40, Step 9 using {trans-3-(4-{[6-[(3-hydroxyazetidin-1-yl)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile as starting materials. LCMS $(M+H)^+$: 609.2.

Example 145. {trans-3-(4-{[6-methyl-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step 1. 6-Methyl-2-(trifluoromethyl)pyrimidin-4(3H)-one

To a solution of 2,2,2-trifluoroethanimidamide (3.02 g, 22.9 mmol) and 3-oxobutanoic acid, methyl ester (2.60 mL, 24.0 mmol) in methanol (25 mL) was added 25 wt% sodium methoxide (10.5 mL, 45.8 mmol). The reaction solution was stirred at room temperature overnight. The solvent was removed *in vacuo* and diluted with ethyl acetate and 5 M HCl. The aqueous layer was extracted with ethyl acetate once. The organic

solutions were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography on a silica gel column to give the desired product as white solid.

Step 2. tert-Butyl 4-{[6-methyl-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate

The title compound was prepared according to the method of Example 40, Step 5 using 6-methyl-2-(trifluoromethyl)pyrimidin-4(3H)-one as starting material. LCMS $(M+H)^+$: 362.2.

Step 3. 4-Methyl-6-(piperidin-4-yloxy)-2-(trifluoromethyl)pyrimidine trifluoroacetate

This compound was prepared according to the method of Example 40, Step 7 using *tert*-butyl 4-{[6-methyl-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate as starting material. LCMS $(M+H)^+$: 333.1.

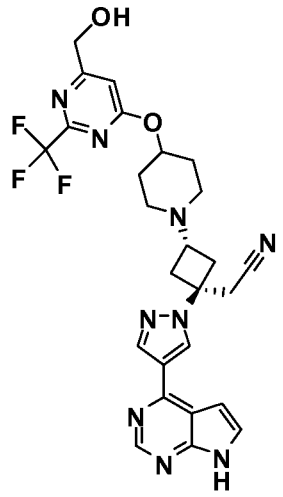
Step 4. {cis-3-(4-{[6-Methyl-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile, {trans-3-(4-{[6-methyl-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

These compounds were prepared according to the method of Example 40, Step 8 using 4-methyl-6-(piperidin-4-yloxy)-2-(trifluoromethyl)pyrimidine trifluoroacetate as starting material. LCMS $(M+H)^+$: 668.3.

Step 5. {trans-3-(4-{[6-Methyl-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

The title compound was prepared according to the method of Example 40, Step 9 using {trans-3-(4-{[6-methyl-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile as starting materials. LCMS $(M+H)^+$: 538.2.

Example 146 {trans-3-(4-{[6-(hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step 1. tert-Butyl 4-{[6-(hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate

To a solution of *tert*-butyl 4-{[6-formyl-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate (202 mg, 0.538 mmol) in methanol (2.0 mL) was added sodium tetrahydroborate (20.4 mg, 0.538 mmol). The reaction solution was stirred at room temperature for 4 hours. The reaction was quenched with water and extracted with ethyl acetate (2x). The organic solutions were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified with silica gel column to give the desired product. LCMS $(M+H)^+$: 378.2.

Step 2. [6-(Piperidin-4-yloxy)-2-(trifluoromethyl)pyrimidin-4-yl]methanol

This compound was prepared according to the method of Example 40, Step 7 using *tert*-butyl 4-{[6-(hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate as starting material. LCMS $(M+H)^+$: 278.2.

Step 3. {cis-3-(4-{[6-(Hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-

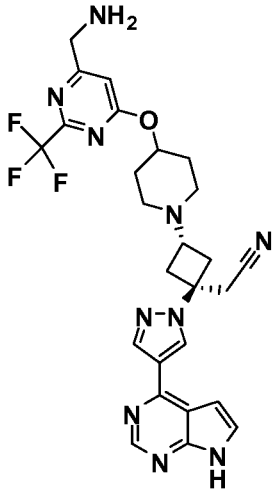
pyrazol-1-yl]cyclobutyl}acetonitrile, {trans-3-(4-{[6-(hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

These compounds were prepared according to the method of Example 40, Step 8 using [6-(piperidin-4-yloxy)-2-(trifluoromethyl)pyrimidin-4-yl]methanol as starting material. LCMS $(M+H)^+$: 684.3.

Step 4. {trans-3-(4-{[6-(Hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

The title compound was prepared according to the method of Example 40, Step 9 using {trans-3-(4-{[6-(hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile as starting materials. LCMS $(M+H)^+$: 554.2.

Example 147 {trans-3-(4-{[6-(aminomethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step 1. [6-[(1-{trans-3-(Cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperidin-4-yl)oxy]-2-(trifluoromethyl)pyrimidin-4-yl]methyl methanesulfonate

To a solution of {trans-3-(4-{[6-(hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (98.5 mg, 0.144 mmol) in DCM (1.0 mL) was added methanesulfonyl chloride (13.4 μL, 0.173 mmol) and *N,N*-diisopropylethylamine (37.6 μL, 0.216 mmol) at 0 °C. The solution was stirred at same temperature for 1 hour. The reaction solution was diluted with DCM and water. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give the desired product. The crude was used in the next without purification. LCMS $(M+H)^+$: 762.2.

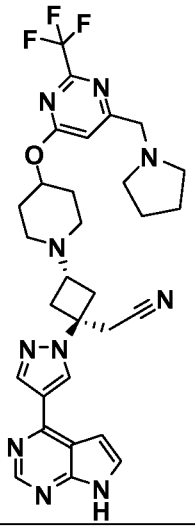
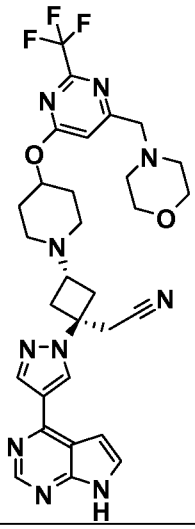
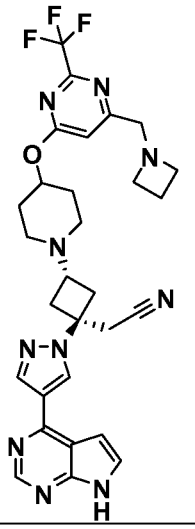
Step 2. {trans-3-(4-{[6-(Aminomethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

To a vial charged with 6-[(1-{trans-3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperidin-4-yl)oxy]-2-(trifluoromethyl)pyrimidin-4-yl]methyl methanesulfonate (23 mg, 0.030 mmol) was added 7.0 M Ammonia in methanol (0.6 mL, 4 mmol). After stirring for 2 h at room temperature, the mixture was concentrated. The residue was treated under the conditions was used in Example 40, Step 9 to give the desired product. LCMS $(M+H)^+$: 553.2.

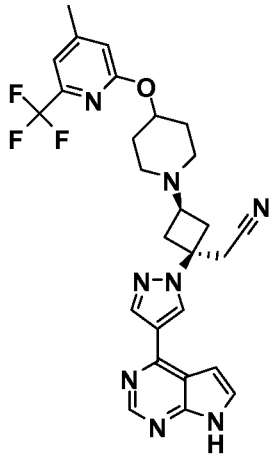
Examples 148-150.

The examples in the table below were made by procedures analogous to those for producing Example 147.

Ex.	Structure	Name	M+H

Ex.	Structure	Name	M+H
148		{trans-3-(4-{[6-(pyrrolidin-1-ylmethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile	607.3
149		{trans-3-(4-{[6-(morpholin-4-ylmethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile	623.3
150		{cis-3-(4-{[6-(azetidin-1-ylmethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile	593.3

Example 151. {trans-3-(4-{[4-methyl-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



Step 1. 4-Methyl-6-(trifluoromethyl)-2H-pyran-2-one

To a solution of trifluoroacetic anhydride (10.63 g, 50.61 mmol) and 3,3-dimethylacryloyl chloride (5.0 g, 42 mmol) in chloroform (85 mL) at 0 °C was added triethylamine (12.91 mL, 92.60 mmol). The resulting reaction mixture was stirred at same temperature for 1 h, then allowed to warm to room temperature overnight. The reaction solution was washed with water (2x), saturated sodium bicarbonate, water, and brine, and then dried over Na_2SO_4, filtered and concentrated. The crude residue was used in next step.

Step 2. 4-Methyl-6-(trifluoromethyl)pyridin-2(1H)-one

To a solution of crude 4-methyl-6-(trifluoromethyl)-2H-pyran-2-one (28.8 g, 162 mmol) in acetic acid (330 mL) was added ammonium acetate (25.0 g, 324 mmol). The reaction solution was heated at 120 °C over weekend.The solvent was removed *in vacuo*. The residue was diluted with ethyl acetate and washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified with pad silica gel. The solvent was removed. The solid was washed with 10: 1 hexanes/ethyl acetate to give the desired product as white solid. LCMS $(M+H)^+$: 178.0.

Step 3. tert-Butyl 4-{[4-methyl-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidine-1-

carboxylate

The title compound was prepared according to the method of Example 40, Step 5 using 4-methyl-6-(trifluoromethyl)pyridin-2(1H)-one as starting material. LCMS $(M+H-56)^+$: 305.1.

Step 4. 4-Methyl-6-(piperidin-4-yloxy)-2-(trifluoromethyl)pyridine

This compound was prepared according to the method of Example 40, Step 7 using *tert*-butyl 4-{[4-methyl-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidine-1-carboxylate as starting material. LCMS $(M+H)^+$: 261.1.

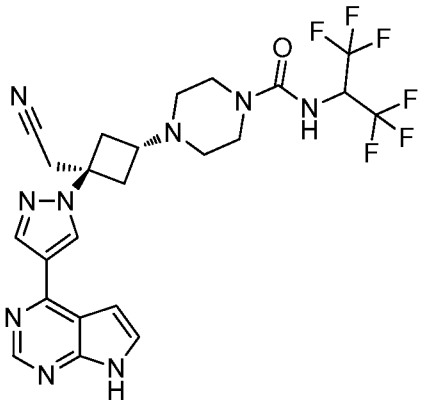
Step 5. {cis-3-(4-{[4-Methyl-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile, {trans-3-(4-{[4-methyl-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

These compounds were prepared according to the method of Example 40, Step 8 using 4-methyl-6-(piperidin-4-yloxy)-2-(trifluoromethyl)pyridine as starting material. LCMS $(M+H)^+$: 667.3.

Step 6. {trans-3-(4-{[4-Methyl-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile

The title compound was prepared according to the method of Example 40, Step 9 using {trans-3-(4-{[4-methyl-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile as starting materials. LCMS $(M+H)^+$: 537.2.

Example 152. 4-{trans-3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]piperazine-1-carboxamide



Step 1. 3,3,3-Trifluoro-2-(trifluoromethyl)propanoyl chloride

3,3,3-Trifluoro-2-(trifluoromethyl)propanoic acid (4.63 g, 23.6 mmol) and phosphorus pentachloride (5.21 g, 25.0 mmol) were stirred for 1 minute, solids were mostly dissolved. The mixture was refluxed for 2 hours and then cooled to room temperature. The acid chloride was isolated by fractional distillation: oil temp: 100 -130 C; vapor temp: 30-35 C. Collected 3.9g colorless liquid (77% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.45 (m, 1H).

Step 2. 1,1,1,3,3,3-Hexafluoro-2-isocyanatopropane

Sodium azide (5.0 g, 77 mmol) in water (15 mL, 830 mmol) and 1,3-dimethyl-benzene (10.0 mL, 81.8 mmol) at 0 °C were added a solution of 3,3,3-trifluoro-2-(trifluoromethyl)propanoyl chloride (1.0 mL, 7.6 mmol) in 1,3-dimethyl-benzene (5 mL, 40 mmol) over 1 minute. After 1 hour, the ice bath was removed. After stirring for 3 hours at room temperature, the organic phase was separated and was dried to give the acyl azide intermediate in xylene. The azide solution was heated at 70 °C for 1 hour to give the isocyanate as a solution in xylene.

Step 3. 4-(3-(Cyanomethyl)-3-(4-(7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)cyclobutyl)-N-(1,1,1,3,3,3-hexafluoropropan-2-yl)piperazine-1-carboxamide

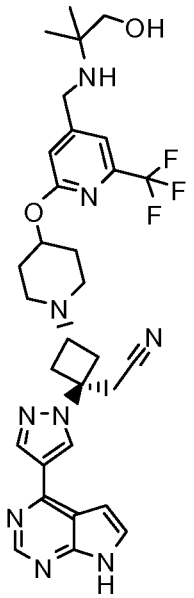
To a solution of {3-piperazin-1-yl-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.10 g, 0.20

mmol) in methylene chloride (5 mL, 80 mmol) was added. 0.21 M 1,1,1,3,3,3-hexafluoro-2-isocyanatopropane in m-xylene (1.2 mL, 0.24 mmol) was added, followed by N,N-diisopropylethylamine (71 μL, 0.41 mmol). The reaction was stirred overnight. The reaction was rotovaped and ethyl acetate was added, washed with sat. NH_4Cl (x2), sat. $NaHCO_3$, and sat. NaCl. The extracts were dried and the solvent removed by rotary evaporation to give 164 mg of an orange oil. The crude oil was purified by column chromatography on 40 g silica gel using a gradient of 0-8% MeOH/DCM, 0-0.8%NH_4Cl. The product was collected as 82mg of a glass (59% yield). LCMS (M+1): 586.

Step 4. 4-{trans-3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]piperazine-1-carboxamide

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)cyclobutyl)-N-(1,1,1,3,3,3-hexafluoropropan-2-yl)piperazine-1-carboxamide in 3 mL DCM and 3 mL TFA was stirred for 1 hour. The solvent was removed by rotary evaporation and the residue was stirred in 3 mL MeOH and 0.3 mL ethylenediamine for 0.5 hour. The reaction purified by LCMS (C18 column eluting with a gradient MeCN/H_2O containing 0.15% NH_4OH at 5 mL/min) to give 43 mg white solid (64% yield). ^1H NMR (400 MHz, dmso) δ 12.12 (Br, 1H), 8.81 (s, 1H), 8.68 (s, 1H), 8.41 (s, 1H), 7.80 (d, J = 9.3 Hz, 1H), 7.59 (d, J = 3.6 Hz, 1H), 7.06 (d, J = 3.6 Hz, 1H), 5.69 (q, J = 8.0 Hz, 1H), 3.46 – 3.39 (m, 5H), 3.05 – 2.95 (m, 2H), 2.78 (t, J = 7.3 Hz, 1H), 2.40 – 2.30 (m, 2H), 2.27 (s, 3H). LCMS (M+1): 556.

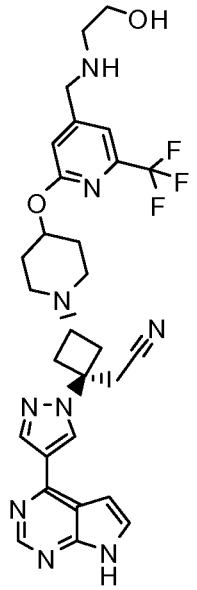
Example 153. {trans-3-(4-{[4-{[(2-hydroxy-1,1-dimethylethyl)amino]methyl}-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



This compound was prepared according to the method of Example 127, using {trans-3-(4-{[4-(hydroxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (25 mg, 0.037 mmol, Peak 1 from Example 123, Step E), N,N-diisopropylethylamine (13 μL, 0.073 mmol) and methanesulphonic anhydride (8.9 mg, 0.051 mmol) in methylene chloride (0.50 mL), followed by 2-amino-2-methyl-1-propanol (52 μL, 0.55 mmol, Fluka) in tetrahydrofuran (0.50 mL) at 50 °C for 1 hour, followed by deprotection (first using 1:1 TFA:DCM, followed by evaporation and then ethylenediamine (0.4 mL) in methanol (2 mL)). Purification under the conditions of Example 127 afforded product as the free base (11 mg, 48%). ^{1}H NMR (400 MHz, dmso) δ 12.13 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.42 (s, 1H), 7.08 (d, J = 3.6 Hz, 1H), 7.06 (s, 1H), 5.04 – 4.91 (m, 1H), 4.58 (t, J = 5.5 Hz, 1H), 3.71 (s, 2H), 3.42 (s, 2H), 3.20 (d, J = 5.0 Hz, 2H), 3.10 – 2.93 (m, 2H), 2.81 (tt, J = 7.4, 7.4 Hz, 1H), 2.70-2.57 (br m, 2H), 2.42 – 2.28 (m, 2H), 2.21-2.10 (br m, 2H), 2.06-1.95 (br m, 2H), 1.73-1.62 (br m, 2H), 0.95 (s, 6H); ^{19}F NMR (376 MHz, dmso) δ -67.25 (s); LCMS $(M+H)^+$: 624.3.

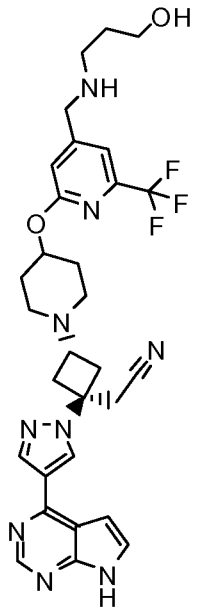
Example 154. {trans-3-(4-{[4-{[(2-hydroxyethyl)amino]methyl}-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-

4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



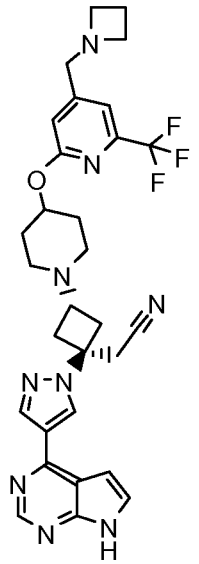
This compound was prepared according to Example 153, using ethanolamine (33 μL, 0.55 mmol, Aldrich) in the displacement step (14 mg, 64%). ^{1}H NMR (400 MHz, dmso) δ 12.13 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, *J* = 3.6 Hz, 1H), 7.42 (s, 1H), 7.08 (d, *J* = 3.6 Hz, 1H), 7.04 (s, 1H), 5.22 – 4.61 (m, 1H), 4.50 (t, *J* = 5.4 Hz, 1H), 3.76 (s, 2H), 3.47 – 3.42 (m, 2H), 3.42 (s, 2H), 3.10 – 2.95 (m, 2H), 2.81 (tt, *J* = 7.4, 7.5 Hz, 1H), 2.72-2.56 (br m, 2H), 2.55 – 2.50 (m, 2H), 2.41 – 2.23 (m, 2H), 2.22-2.08 (br m, 2H), 2.06-1.93 (br m, 2H), 1.75-1.60 (br m, 2H); ^{19}F NMR (376 MHz, dmso) δ -67.28 (s); LCMS $(M+H)^+$: 596.3.

Example 155. {trans-3-(4-{[4-{[(3-hydroxypropyl)amino]methyl}-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



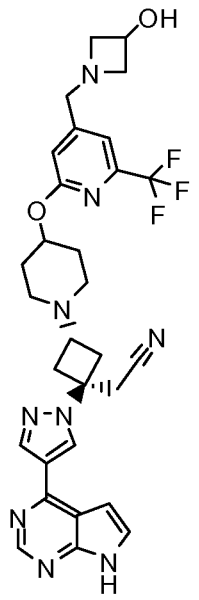
The procedure of Example 153 was followed, using 3-amino-1-propanol (42 μL, 0.55 mmol, Aldrich) overnight at room temperature (13 mg, 58%). ^{1}H NMR (400 MHz, dmso) δ 12.13 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, *J* = 3.6 Hz, 1H), 7.42 (s, 1H), 7.08 (d, *J* = 3.6 Hz, 1H), 7.03 (s, 1H), 5.13 – 4.67 (m, 1H), 4.41 (br s, 1H), 3.72 (s, 2H), 3.49 – 3.38 (m, 4H), 3.10 – 2.94 (m, 2H), 2.81 (tt, *J* = 7.51, 7.52 Hz, 1H), 2.72 – 2.55 (m, 2H), 2.52 – 2.47 (m, 2H), 2.41 – 2.27 (m, 2H), 2.23-2.08 (br m, 2H), 2.07-1.94 (br m, 2H), 1.80 – 1.61 (m, 2H), 1.56 (tt, *J* = 6.6, 6.7 Hz, 2H); ^{19}F NMR (376 MHz, dmso) δ -67.28 (s); LCMS $(M+H)^+$: 610.1.

Example 156. {trans-3-(4-{[4-(azetidin-1-ylmethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



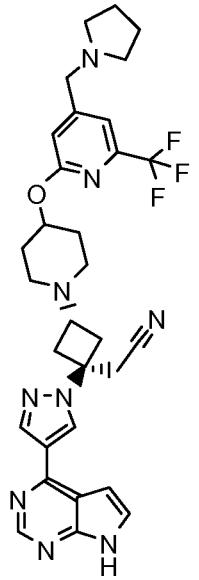
The procedure of Example 153 was followed, using azetidine (37 μL, 0.55 mmol, Aldrich) overnight at room temperature (9 mg, 40%). ^{1}H NMR (400 MHz, dmso) δ 12.13 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.31 (s, 1H), 7.08 (d, J = 3.6 Hz, 1H), 6.94 (s, 1H), 5.21 – 4.67 (m, 1H), 3.59 (s, 2H), 3.42 (s, 2H), 3.16 (t, J = 7.0 Hz, 4H), 3.07 – 2.93 (m, 2H), 2.81 (tt, J = 7.4 Hz, 1H), 2.70 – 2.55 (m, 2H), 2.40 – 2.25 (m, 2H), 2.23 – 2.07 (m, 2H), 2.07 – 1.92 (m, 4H), 1.74 – 1.59 (m, 2H); ^{19}F NMR (376 MHz, dmso) δ -67.37 (s); LCMS $(M+H)^+$: 592.1.

Example 157. {trans-3-(4-{[4-[(3-hydroxyazetidin-1-yl)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



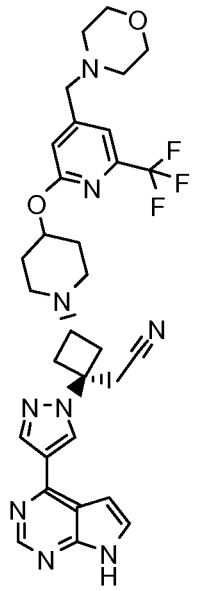
The procedure of Example 153 was followed, using N,N-diisopropylethylamine (64 μL, 0.37 mmol) and azetidin-3-ol hydrochloride (30 mg, 0.3 mmol, Oakwood) in the displacement step. After stirring overnight at room temperature, methanol (0.20 mL) was added to afford a homogenous solution, which was stirred for a further 2.5 hours at room temperature and treated according to the deprotection and purification conditions given in Example 153 to afford product as the free base (9.7 mg, 44%).^{1}H NMR (400 MHz, dmso) δ 12.12 (br s, 1H), 8.81 (s, 1H), 8.67 (s, 1H), 8.40 (s, 1H), 7.59 (d, J = 3.6 Hz, 1H), 7.29 (s, 1H), 7.06 (d, J = 3.6 Hz, 1H), 6.93 (s, 1H), 5.34 (d, J = 6.4 Hz, 1H), 5.05 – 4.77 (m, 1H), 4.19 (h, J = 6.1 Hz, 1H), 3.60 (s, 2H), 3.50 (td, J = 6.1, 2.0 Hz, 2H), 3.40 (s, 2H), 3.06 – 2.92 (m, 2H), 2.86 – 2.71 (m, 3H), 2.68 – 2.53 (m, 2H), 2.38 – 2.22 (m, 2H), 2.22-2.07 (br m, 2H), 2.05-1.95 (br m, 2H), 1.75 – 1.48 (m, 2H); ^{19}F NMR (376 MHz, dmso) δ -67.36 (s); LCMS $(M+H)^+$: 608.2.

Example 158. {trans-3-(4-{[4-(pyrrolidin-1-ylmethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



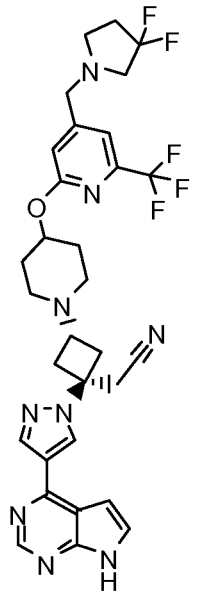
The method of Example 127 was followed, except that the displacement of mesylate with amine was carried out with pyrrolidine (10 μL, 0.2 mmol, Aldrich) in methanol (0.30 mL) at room temperature for one hour. The deprotection was carried out as described in that example, but 0.3 mL of ethylenediamine was used. The product was obtained in pure form as the free base by the method described in that example (8.7 mg, 65%). ^{1}H NMR (400 MHz, dmso) δ 12.12 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.36 (s, 1H), 7.08 (d, J = 3.6 Hz, 1H), 7.00 (s, 1H), 5.00 (tt, J = 7.6, 3.8 Hz, 1H), 3.64 (s, 2H), 3.42 (s, 2H), 3.09 – 2.94 (m, 2H), 2.81 (tt, J = 7.4, 7.4 Hz, 1H), 2.71-2.57 (br m, 2H), 2.47 – 2.40 (m, 4H), 2.38 – 2.27 (m, 2H), 2.23-2.08 (br m, 2H), 2.06-1.95 (br m, 2H), 1.81 – 1.49 (m, 6H); ^{19}F NMR (376 MHz, dmso) δ -67.32 (s); LCMS $(M+H)^+$: 606.1.

Example 159. {trans-3-(4-{[4-(morpholin-4-ylmethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



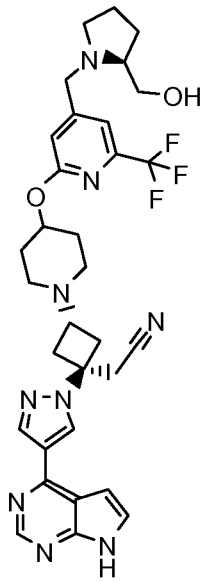
This compound was prepared according to method of Example 158, using Morpholine (20 μL, 0.2 mmol, Aldrich) in the displacement step, for 1 hour at room temperature (8.1 mg, 59%). ^{1}H NMR (400 MHz, dmso) δ 12.12 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, *J* = 3.6 Hz, 1H), 7.38 (s, 1H), 7.08 (d, *J* = 3.6 Hz, 1H), 7.02 (s, 1H), 5.00 (tt, *J* = 8.1, 3.8 Hz, 1H), 3.58 (dd, *J* = 4.6 Hz, 4H), 3.55 (s, 2H), 3.41 (s, 2H), 3.08 – 2.92 (m, 2H), 2.81 (tt, *J* = 7.4, 7.4 Hz, 1H), 2.71-2.57 (br m, 2H), 2.42 – 2.25 (m, 6H), 2.23-2.08 (br m, 2H), 2.07-1.94 (br m, 2H), 1.76 – 1.57 (m, 2H); ^{19}F NMR (376 MHz, dmso) δ -67.33 (s); LCMS $(M+H)^+$: 622.2.

Example 160. {trans-3-(4-{[4-[(3,3-difluoropyrrolidin-1-yl)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



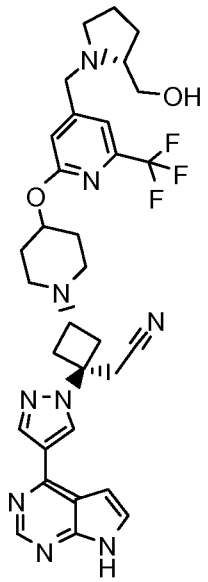
The method of Example 158 was followed, except that the displacement of mesylate with amine was carried out using 3,3-difluoropyrrolidine hydrochloride (20 mg, 0.2 mmol, Oakwood), and N,N-diisopropylethylamine (30 μL, 0.2 mmol) at room temperature overnight (5.6 mg, 40%). ^{1}H NMR (400 MHz, dmso) δ 12.13 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.45 – 7.31 (m, 1H), 7.08 (d, J = 3.6 Hz, 1H), 7.02 (s, 1H), 5.26 – 4.62 (m, 1H), 3.70 (s, 2H), 3.42 (s, 2H), 3.09 – 2.96 (m, 2H), 2.90 (t, J = 13.3 Hz, 2H), 2.81 (tt, J = 7.7, 7.8 Hz, 1H), 2.72 (t, J = 7.0 Hz, 2H), 2.69 – 2.56 (m, 2H), 2.45 – 2.09 (m, 6H), 2.07-1.94 (br m, 2H), 1.77 – 1.58 (m, 2H); ^{19}F NMR (376 MHz, dmso) δ -67.35 (s), -91.48 (p, J = 14.4 Hz); LCMS $(M+H)^+$: 642.1.

Example 161. {trans-3-(4-{[4-{[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl}-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



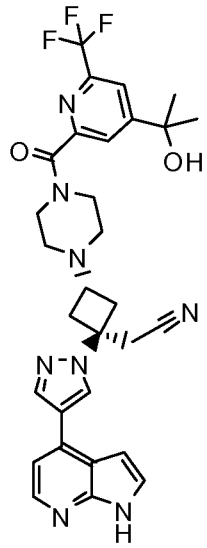
The method of Example 158 was followed, except that the displacement of mesylate with amine was carried out using (2*S*)-pyrrolidin-2-ylmethanol (20 μL, 0.2 mmol, Aldrich), at room temperature overnight (8.3 mg, 59%). ^{1}H NMR (500 MHz, DMSO) δ 12.09 (br s, 1H), 8.81 (s, 1H), 8.69 (s, 1H), 8.41 (s, 1H), 7.59 (d, *J* = 3.5 Hz, 1H), 7.39 (s, 1H), 7.06 (d, *J* = 3.6 Hz, 1H), 7.03 (s, 1H), 5.00 (tt, *J* = 8.4, 3.9 Hz, 1H), 4.48 (s, 1H), 4.12 (d, *J* = 14.8 Hz, 1H), 3.45 (d, *J* = 15.0 Hz, 1H), 3.41 (s, 2H), 3.42-3.25 (m, 2H), 3.06 – 2.97 (m, 2H), 2.87 – 2.77 (m, 2H), 2.69 – 2.62 (m, 2H), 2.59 (dddd, *J* = 5.8, 5.8, 5.8, 8.1 Hz, 1H), 2.41 – 2.31 (m, 2H), 2.22 – 2.09 (m, 3H), 2.08 – 1.95 (m, 2H), 1.83 (dddd, *J* = 8.1, 8.1, 8.3, 12.2 Hz, 1H), 1.75 – 1.46 (m, 5H); ^{19}F NMR (376 MHz, dmso) δ -67.24 (s); LCMS $(M+H)^+$: 636.3.

Example 162. {trans-3-(4-{[4-{[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl}-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



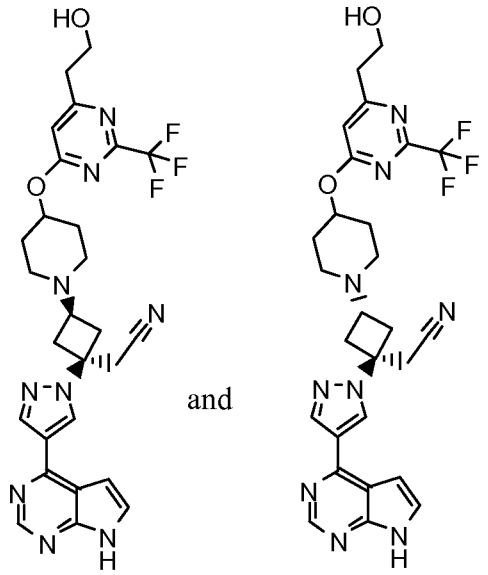
The method of Example 158 was followed, except that the displacement of mesylate with amine was carried out using (2*R*)-pyrrolidin-2-ylmethanol (20 μL, 0.2 mmol, Aldrich) at room temperature overnight (8.3 mg, 59%). ^{1}H NMR (400 MHz, dmso) δ 12.14 (br s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, *J* = 3.6 Hz, 1H), 7.39 (s, 1H), 7.08 (d, *J* = 3.6 Hz, 1H), 7.03 (s, 1H), 5.04 – 4.94 (m, 1H), 4.52 (t, *J* = 5.4 Hz, 1H), 4.12 (d, *J* = 14.9 Hz, 1H), 3.52 – 3.22 (m, 5H), 3.09 – 2.92 (m, 2H), 2.86 – 2.73 (m, 2H), 2.70 – 2.53 (m, 3H), 2.42 – 2.27 (m, 2H), 2.22 – 2.09 (m, 3H), 2.06 – 1.87 (m, 2H), 1.82 (dddd, *J* = 8.0, 8.0, 8.4, 11.9 Hz, 1H), 1.77 – 1.37 (m, 5H); ^{19}F NMR (376 MHz, dmso) δ -67.24 (s); LCMS $(M+H)^+$: 636.3.

Example 163. {trans-3-(4-{[4-(1-hydroxy-1-methylethyl)-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile



4-(1-Hydroxy-1-methylethyl)-6-(trifluoromethyl)pyridine-2-carboxylic acid (0.0125 g, 0.0501 mmol, from Example 75, Step D) was dissolved in N,N-dimethylformamide (1 mL) and to this was added {trans-3-piperazin-1-yl-1-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (0.0250 g, 0.0508 mmol, obtained by treatment of Peak 2 of Step D from Example 77 with the conditions found in Step E of Example 77) , followed by benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (26.57 mg, 0.06008 mmol) and Triethylamine (0.035 mL, 0.25 mmol). The reaction was stirred for 6 hours and was worked up by partitioning between ethyl acetate and brine. The aqueous portion was extracted a total of 3 times with ethyl acetate. The combined extracts were washed with water twice, then brine, dried over sodium sulfate, filtered and concentrated. The crude product was deprotected by stirring with TFA:DCM (1:1) for 1 hour, evaporated, then with ethylenediamine (1.5 mL) in methanol overnight. Purification by preparative HPLC-MS (C18, eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) afforded product as the free base (0.01 g, 30%). ^1H NMR (300 MHz, CD_3OD) δ 8.53 (d, J = 0.7 Hz, 1H), 8.20 (s, J = 0.7 Hz, 1H), 8.15 (d, J = 5.2 Hz, 1H), 7.99 (d, J = 1.6 Hz, 1H), 7.97 – 7.92 (m, 1H), 7.43 (d, J = 3.6 Hz, 1H), 7.31 (d, J = 5.2 Hz, 1H), 6.82 (d, J = 3.6 Hz, 1H), 3.99 – 3.74 (m, 2H), 3.64 – 3.47 (m, 2H), 3.17 – 3.01 (m, 2H), 2.96 (tt, J = 6.7, 7.0 Hz, 1H), 2.60 – 2.40 (m, 6H), 1.55 (s, 6H); ^{19}F NMR (282 MHz, CD_3OD) δ -69.03 (s); LCMS $(M+H)^+$: 593.1.

Example 164. {cis-3-(4-{[6-(2-hydroxyethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile and {trans-3-(4-{[6-(2-hydroxyethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (each diastereomer isolated)



Step 1. Methyl [6-hydroxy-2-(trifluoromethyl)pyrimidin-4-yl]acetate

2,2,2-Trifluoroethanimidamide (6.7 g, 50. mmol, Oakwood) was dissolved in 0.5 M sodium methoxide in methanol (120 mL, 60. mmol) and 3-oxo-pentanedioic acid dimethyl ester (8.4 mL, 55 mmol, Aldrich) was added. The reaction solution was stirred at room temperature for 72 hours, followed by heating to 50 °C for 42 hours. The solvent was removed *in vacuo*. 1 N HCl (50mL) was added, this resulted in pH 5. After stirring overnight, 4 M HCl (10mL) and ethyl acetate were added, and layers separated. The aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried over sodium sulfate, filtered and concentrated. Flash chromatography, on 120 g silica gel cartridge, eluting with a gradient (solvent A= hexane; solvent B= 3% iPrOH/EtOAc) from 0-30% solvent B in A over 40 minutes and hold at 30% for 20 minutes at a flow rate of 60 mL/min. The residue obtained on

evaporation of product-containing fractions was mixed with DCM and the resulting white ppt (impurity) was removed by filtration. The filtrate was evaporated and the resulting residue was repurified (A= hexane; solvent B= iPrOH) on a 120 g silica gel cartridge, eluting with a gradient from 0-20% B in A over 25 minutes and hold at 20% B at a flow rate of 60 mL/min. Evaporated to afford an oil which crystallized on standing (5.2 g, 75% pure). A portion of the material was purified via preparative HPLC-MS (C18, eluting with a gradient of MeCN/H_2O containing 0.1% TFA) to afford product used in the subsequent step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (s, 1H), 3.76 (s, 3H), 3.75 (s, 2H).

Step 2. tert-Butyl 4-{[6-(2-methoxy-2-oxoethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate

To tert-butyl 4-hydroxypiperidine-1-carboxylate (213 mg, 1.06 mmol, Aldrich) in tetrahydrofuran (2.0 mL) was added Triphenylphosphine (0.284 g, 1.08 mmol) , followed by diisopropyl azodicarboxylate (0.215 mL, 1.09 mmol). After 10 minutes, methyl [6-hydroxy-2-(trifluoromethyl)pyrimidin-4-yl]acetate (0.20 g, 0.85 mmol, from Step 1) was added. The reaction was stirred for 1 hour and solvent was removed *in vacuo*. Flash chromatography on a 40 g silica gel cartridge, eluting with a gradient from 0-20% EtOAc in hexanes afforded product as a viscous oil (127 mg, 25%). LCMS $(M+H)^+$: 420.0.

Step 3. tert-Butyl 4-{[6-(2-hydroxyethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate

Sodium tetrahydroborate (32 mg, 0.83 mmol) was added to a solution of tert-butyl 4-{[6-(2-methoxy-2-oxoethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate (125 mg, 0.209 mmol, from Step 2) in tetrahydrofuran (2.0 mL). Methanol (0.21 mL) was added in portions. After stirring for 2 hours, the mixture was quenched by the addition of saturated ammonium chloride solution. The reaction was diluted with additional water, and the product was extracted with EtOAc. The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. Flash chromatography on a 12 g silica gel column, eluting with a gradient from 0-30% EtOAc in hexanes afforded product (26 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (s, 1H),

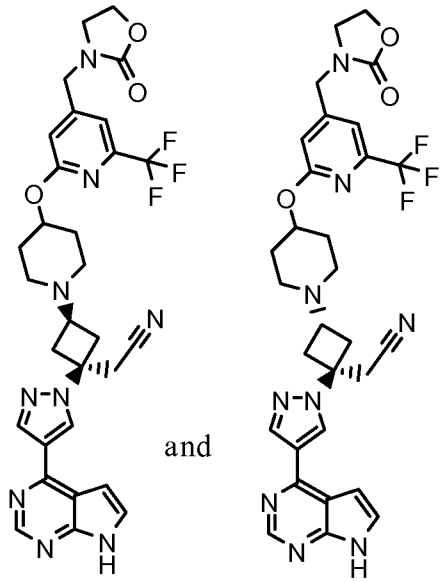
5.35 (tt, J = 7.8, 3.7 Hz, 1H), 4.07 – 3.96 (m, 2H), 3.81 – 3.61 (m, 2H), 3.31 (ddd, J = 13.5, 8.4, 3.7 Hz, 2H), 2.99 (t, J = 5.4 Hz, 2H), 2.03 – 1.92 (m, 2H), 1.79 – 1.68 (m, 2H), 1.47 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -71.37 (s); LCMS $(M+Na)^+$: 414.0.

Step 4. {cis-3-(4-{[6-(2-hydroxyethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile and {trans-3-(4-{[6-(2-hydroxyethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (each diastereomer isolated)

tert-Butyl 4-{[6-(2-hydroxyethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidine-1-carboxylate (26.0 mg, 0.0664 mmol, from Step 3) was dissolved in 4.0 M hydrogen chloride in dioxane (0.50 mL, 2.0 mmol) and the mixture was stirred for 30 minutes. The mixture was neutralized by the addition of saturated sodium bicarbonate solution and was extracted with DCM (6 times). The combined extracts were dried over sodium sulfate, filtered and concentrated. Sodium cyanoborohydride (5.9 mg, 0.093 mmol) and zinc dichloride (6.3 mg, 0.046 mmol) were combined in methanol (0.34 mL) and stirred for two hours. Following this, the deprotected piperidine, generated above, and {3-oxo-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (34 mg, 0.080 mmol, from Step 7 of Example 1a) were mixed in methanol (0.95 mL) and stirred to dissolve, then the reducing mixture generated by the combination of sodium cyanoborohydride and zinc dichloride was added. The reaction was stirred overnight, then was diluted with DCM and washed with saturated sodium bicarbonate solution. The aqueous phase was extracted with two further portions of DCM, the combined extracts were dried over sodium sulfate, filtered and concentrated. The residue was dissolved in a 1:1 mixture of TFA:DCM, stirred for one hour, then concentrated, re-dissolved in 2.0 mL methanol, and 0.20 mL ethylenediamine was added. Purification via preparative HPLC-MS (C18, eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) afforded 12 mg product, as a mixture of cis- and trans- isomers, 32% yield. Chiral HPLC was used to separate the isomers (Phenomenex Lux Cellulose-2, 21.1 x 250mm, eluting with 45% EtOH in hexanes at 18

mL/min, 6 mg per injection). Peak 1, trans isomer, eluted at 8.84 minutes (4.6 mg, 12% overall yield). ^{1}H NMR (400 MHz, dmso) δ 12.13 (br s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.40 (s, 1H), 7.60 (d, *J* = 3.6 Hz, 1H), 7.09 (s, 1H), 7.07 (d, *J* = 3.6 Hz, 1H), 5.11 (tt, *J* = 8.6, 3.7 Hz, 1H), 4.74 (t, *J* = 5.2 Hz, 1H), 3.79-3.72 (m, 2H), 3.47 (s, 2H), 2.94 (tt, *J* = 7.7, 7.8 Hz, 1H), 2.86 (t, *J* = 6.3 Hz, 2H), 2.71 – 2.54 (m, 6H), 2.28 – 2.10 (m, 2H), 2.07 – 1.89 (m, 2H), 1.81 – 1.59 (m, 2H); ^{19}F NMR (376 MHz, dmso) δ -69.87 (s); LCMS $(M+H)^+$: 568.0; Peak 2, cis isomer, eluted at 12.55 minutes (4.3 mg, 11% overall yield). ^{1}H NMR (400 MHz, dmso) δ 12.13 (s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, *J* = 3.6 Hz, 1H), 7.13 – 6.99 (m, 2H), 5.10 (tt, *J* = 9.0, 4.3 Hz, 1H), 4.74 (t, *J* = 5.3 Hz, 1H), 3.78-3.72 (m, 2H), 3.42 (s, 2H), 3.06 – 2.96 (m, 2H), 2.86 (t, *J* = 6.2 Hz, 2H), 2.81 (tt, *J* = 7.4, 7.4 Hz, 1H), 2.70 – 2.55 (m, 2H), 2.40 – 2.30 (m, 2H), 2.26 – 2.12 (m, 2H), 2.08 – 1.96 (m, 2H), 1.79 – 1.63 (m, 2H); ^{19}F NMR (376 MHz, dmso) δ -69.87 (s); LCMS $(M+H)^+$: 568.0.

Example 165. {cis-3-(4-{[4-[(2-oxo-1,3-oxazolidin-3-yl)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile and {trans-3-(4-{[4-[(2-oxo-1,3-oxazolidin-3-yl)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (each diastereomer isolated)



Step 1. tert-Butyl 2-chloro-6-(trifluoromethyl)isonicotinate

2-Chloro-6-(trifluoromethyl)pyridine (20.00 g, 110.2 mmol, Oakwood) was dissolved in tetrahydrofuran (400 mL) and 1.0 M lithium chloride - chloro(2,2,6,6-tetramethylpiperidin-1-yl)magnesium (1:1) in THF (132.2 mL, 132.2 mmol, Aldrich) was added at 25 °C. The reaction was stirred at 25 °C for 1 hour and was cooled to -78 °C, and di-tert-butyldicarbonate (48.1 g, 220 mmol, Aldrich) in tetrahydrofuran (135 mL) was added. The reaction was allowed to warm to room temperature, and after the reaction was complete as determined by analytical LCMS, the reaction was quenched by the addition of saturated NH_4Cl solution and the product was extracted with EtOAc. The combined organic extracts were washed with 1N HCl, satd. $NaHCO_3$ solution, dried over sodium sulfate, filtered and the solvents were removed in vacuo. Flash chromatography on silica gel eluting with 5% EtOAc/hexanes afforded desired product as a light yellow solid (14.0 g, 45%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 1.2 Hz, 1H), 8.01 (dq, J = 1.1, 0.6 Hz, 1H), 1.62 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -68.43 (s); LCMS $(M+H)^+$: 282.0.

Step 2. tert-Butyl 4-{[4-(hydroxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidine-1-carboxylate

To a mixture of sodium hydride (1.1 g, 28 mmol, 60% in mineral oil) in

tetrahydrofuran (45 mL) at 0 °C was added tert-butyl 4-hydroxypiperidine-1-carboxylate (5.8 g, 29 mmol, Aldrich). The mixture was then stirred at room temperature for 50 minutes. A solution of tert-butyl 2-chloro-6-(trifluoromethyl)isonicotinate (3.0 g, 11 mmol, from Step 1) in tetrahydrofuran (15 mL) was added, and the mixture was stirred at rt over three nights. The mixture was then quenched by the addition of 15 mL of 1N NaOH. After stirring for 2 hours, the mixture was further diluted with water and extracted with two portions of diethyl ether. The aqueous layer was acidified to pH 6 by the addition of conc. HCl, solid sodium chloride was added to saturate and the product was extracted with EtOAc (3x). The combined extracts were dried over sodium sulfate, filtered and concentrated to afford 4.2 g of yellow solid. The solid was dissolved in methanol (100 mL) and cooled to 0 °C. A solution of 2.0 M trimethylsilyldiazomethane in ether was added in sufficient quantity to effect complete conversion to the methyl ester as determined by TLC and analytical LCMS. Excess reagent was quenched by the addition of acetic acid to the mixture which was still at 0 °C. Saturated sodium bicarbonate solution was introduced to achieve pH in the range of 7-8 and brine was also added. The product was extracted in one portion of EtOAc and this extract was dried over sodium sulfate, filtered and concentrated to afford a yellow solid. Sodium tetrahydroborate (1.2 g, 32 mmol) was added to a solution of this product in ethanol (60. mL) at 0 °C, and the reaction mixture was allowed to warm to room temperature and stir for 3.5 hours. The reaction was quenched by the addition of saturated ammonium chloride solution. The mixture was further diluted with water and extracted with two portions of EtOAc. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated. The alcohol product was purified by flash chromatography on silica gel (120 g), eluting with a gradient of 0-40% EtOAc in hexanes to afford the product as a colorless oil (2.8 g, 70%). LCMS $(M+Na)^+$: 399.1.

Step 3. tert-Butyl 4-{[4-[(2-oxo-1,3-oxazolidin-3-yl)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidine-1-carboxylate

Triethylamine (220 μL, 1.6 mmol) and then methanesulfonyl chloride (82 μL, 1.1 mmol) were added to a solution of tert-butyl 4-{[4-(hydroxymethyl)-6-

(trifluoromethyl)pyridin-2-yl]oxy}piperidine-1-carboxylate (0.20 g, 0.53 mmol, from Step 2) in methylene chloride (2 mL) at 0 °C. After stirring at this temperature for 30 minutes, the reaction mixture was partitioned between water and EtOAc. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude mesylate intermediate was dissolved in N,N-dimethylformamide (2.0 mL), and oxazolidin-2-one (230 mg, 2.6 mmol) was added. The mixture was cooled to 0 °C and sodium hydride (53 mg, 1.3 mmol, 60% in mineral oil) was added. The reaction was warmed to room temperature and stirred for 40 minutes, then was quenched with water, and extracted with EtOAc. The organic extract was washed with water, brine, dried over sodium sulfate, filtered and concentrated. Flash chromatography, eluting with a gradient from 0-70% EtOAc in hexanes afforded product (95 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.79 (s, 1H), 5.27 (tt, J = 7.7, 4.1 Hz, 1H), 4.44 (s, 2H), 4.44 – 4.38 (m, 2H), 3.80 – 3.68 (m, 2H), 3.58 – 3.47 (m, 2H), 3.31 (ddd, J = 13.6, 8.5, 3.6 Hz, 2H), 1.99 (ddt, J = 13.2, 6.3, 3.0 Hz, 2H), 1.78 – 1.67 (m, 2H), 1.47 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.89 (s); LCMS $(M+Na)^+$: 468.0.

Step 4. {cis-3-(4-{[4-[(2-oxo-1,3-oxazolidin-3-yl)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile and {trans-3-(4-{[4-[(2-oxo-1,3-oxazolidin-3-yl)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (each diastereomer isolated)

tert-Butyl 4-{[4-[(2-oxo-1,3-oxazolidin-3-yl)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidine-1-carboxylate (93 mg, 0.21 mmol, from Step 3) was dissolved in 4.0 M hydrogen chloride in dioxane (1.6 mL, 6.3 mmol) and was stirred for 30 minutes. The mixture was neutralized with saturated sodium bicarbonate solution, then extracted with chloroform (6x). The combined extracts were dried over sodium sulfate, filtered and concentrated. The crude product and {3-oxo-1-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile (97 mg, 0.23 mmol, from Step 7 of Example 1a) were mixed in methanol (3.0 mL) and stirred to dissolve, then a solution prepared from the combination of sodium cyanoborohydride (18

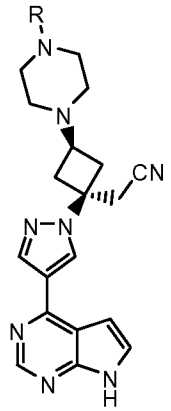
mg, 0.29 mmol) and zinc dichloride (20. mg, 0.15 mmol) in methanol (1.1 mL) that had been pre-stirred for 50 minutes was added. After stirring for 3 hours, the SEM-protected cis- and trans- intermediates were purified and isolated separately via preparative HPLC-MS (Waters XBridge, 30 x 100 mm, eluting with a gradient over 12 minutes from 45.7 to 63.7% MeCN in H_2O containing 0.15% NH_4OH). Peak 1 retention time: 9.5 min, Peak 2 retention time: 10.3 min. After evaporating solvent, each of Peak 1 and Peak 2 were deprotected separately by stirring in a 1:1 mixture of TFA:DCM for one hour, evaporation, then stirring in 2.0 mL methanol containing 0.20 mL ethylenediamine until deprotection was complete as determined by analytical LCMS. Purification of deprotected Peak 1 via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) afforded the cis- isomer (16.8 mg, 13% yield). ^{1}H NMR (400 MHz, dmso) δ 12.13 (br s, 1H), 8.70 (s, 1H), 8.68 (s, 1H), 8.39 (d, J = 0.6 Hz, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.36 (d, J = 0.6 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 7.00 (s, 1H), 5.02 (ddd, J = 11.6, 7.5, 3.4 Hz, 1H), 4.43 (s, 2H), 4.38 – 4.27 (m, 2H), 3.55 – 3.49 (m, 2H), 3.47 (s, 2H), 2.93 (tt, J = 7.5, 7.6 Hz, 1H), 2.70 – 2.56 (m, 6H), 2.27 – 2.09 (m, 2H), 2.06 – 1.94 (m, 2H), 1.74 – 1.60 (m, 2H); ^{19}F NMR (376 MHz, dmso) δ -67.40 (s); LCMS $(M+H)^+$: 622.2. Purification of deprotected Peak 2 via preparative HPLC-MS (C18 eluting with a gradient of MeCN/H_2O containing 0.15% NH_4OH) afforded the trans- isomer (21.6 mg, 17% yield). ^{1}H NMR (400 MHz, dmso) δ 12.13 (s, 2H), 8.83 (s, 1H), 8.69 (s, 1H), 8.42 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.36 (s, 1H), 7.08 (d, J = 3.6 Hz, 1H), 6.99 (s, 1H), 5.05 – 4.97 (m, 1H), 4.43 (s, 2H), 4.38 – 4.27 (m, 2H), 3.57 – 3.47 (m, 2H), 3.42 (s, 2H), 3.13 – 2.90 (m, 2H), 2.82 (tt, J = 7.4, 7.5 Hz, 1H), 2.72 – 2.58 (m, 2H), 2.42 – 2.29 (m, 2H), 2.24 – 2.09 (m, 2H), 2.09 – 1.88 (m, 2H), 1.78 – 1.62 (m, 2H); ^{19}F NMR (376 MHz, dmso) δ -67.40 (s); LCMS $(M+H)^+$: 622.2.

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) and JAK2 (a.a. 828-1132) with an N-terminal His tag were expressed using baculovirus in insect cells and

purified. The catalytic activity of JAK1 and JAK2 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 Tables A-F for data related to compounds of the Examples (at 1 mM). Data is indicated as ranges, wherein "+" is less than 10 nM; "++" is 10 nM to 25 nM; "+++" is greater than 25 nM to 100 nM; and "++++" is greater than 100 nM. Greater than 25 nM to 100 nM specifies a range with a lower endpoint "at greater than 25 nM" and an upper endpoint at 100 nM.

Table A



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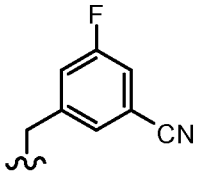
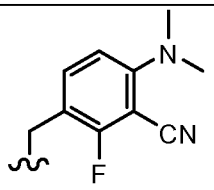
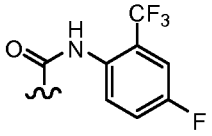
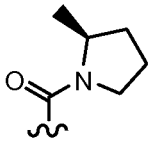
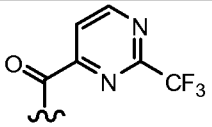
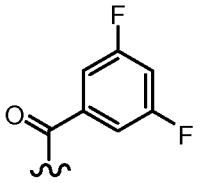
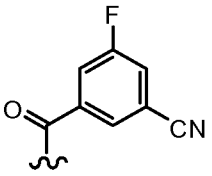
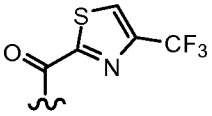
Ex No.	R=	JAK1 IC_{50} (nM)	JAK2 IC_{50} (nM)
1a		+	++++
2a		+	+++
3a		+++	++++
4a		+++	++++
6a		++	++++
7a		++	++++
8a		+	+++
12a		+	+++
13a		+	+++

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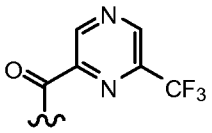
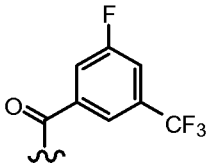
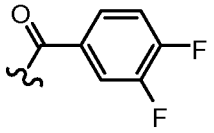
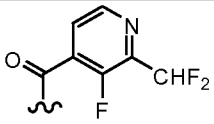
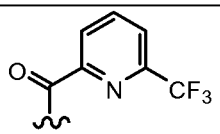
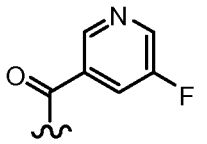
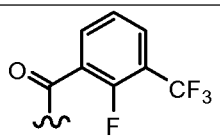
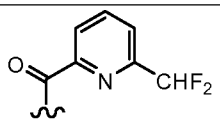
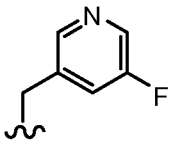
14a		+	+++
17		+	+++
15a		+	+++
11a		++	++++
20a		+	+++
10a		+	++++
22		+	+++
21a		+	+++
23a		++	++++

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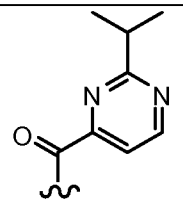
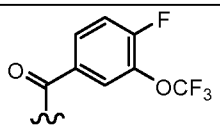
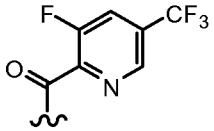
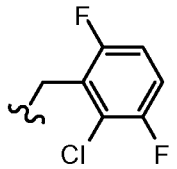
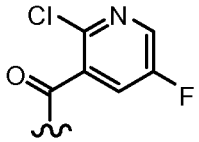
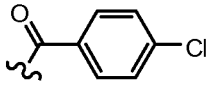
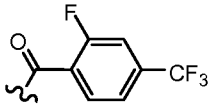
24a		++	++++
26		++	+++
27		+	+++
16a		+	++
9a		++	++++
28		+	++
29		++	+++

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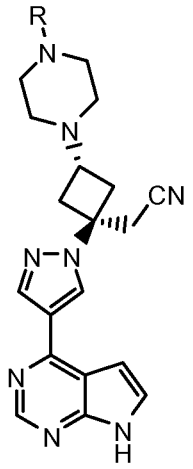

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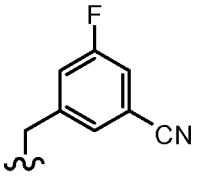
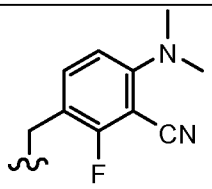
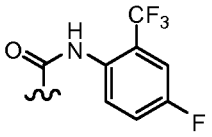
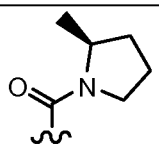
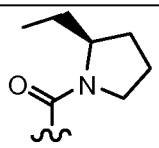
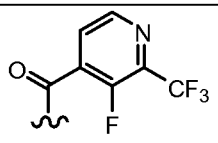
1b		+	+++
2b		+	+++
3b		++	++++
4b		+	++++
5		+	++++
6b		+	+++

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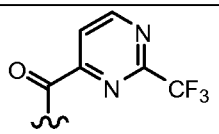
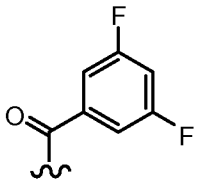
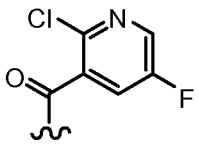
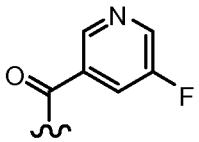
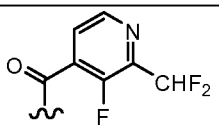
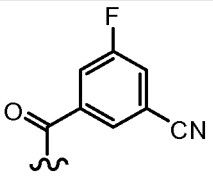
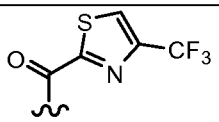
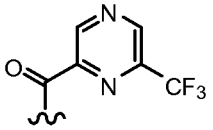
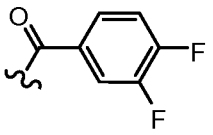
7b		+	+++
8b		+	+
9b		+	++
10b		+	+++
11b		+	+++
12b		+	++
13b		+	+++
14b		+	+++
15b		+	++

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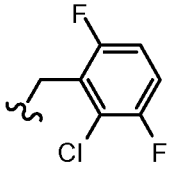
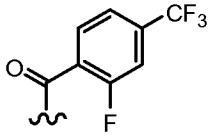
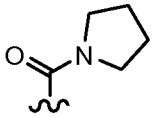
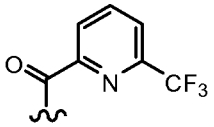
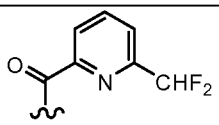
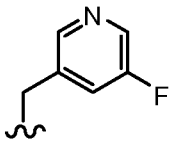
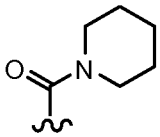
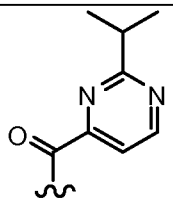
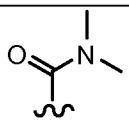
16b		+	+++
18		+	++
19		++	++++
20b		+	+++
21b		+	++
23b		+	+++
25		+++	++++
24b		++	+++
32		+	++++

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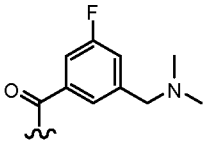
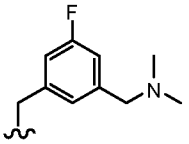
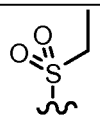
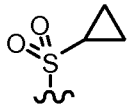
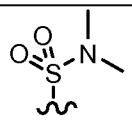
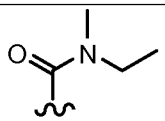
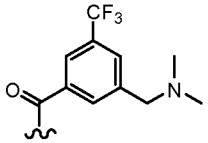
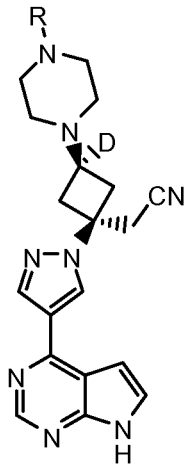
33		+	+
34		+	++
35		+	+
36		+	+
37		+	+
38		+	+++
39		+	+++

Table C



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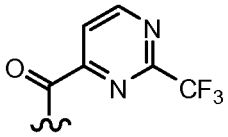
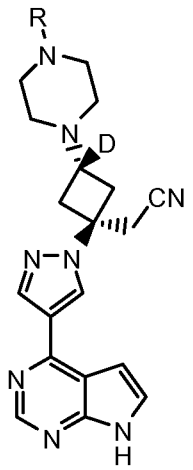
30		+	++++

Table D



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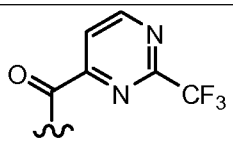
31		+	+++

Table E

Ex. No.	Salt Form	JAK1 IC_{50} (nM) at 1 mM	JAK2 IC_{50} (nM) +
40, isomer 1	-	+	++
40, isomer 2	-	+	+
41, isomer 1	-	+	++
41, isomer 2	-	+	+

Table F

Example	JAK1 IC_{50} (nM) at 1 mM ATP	JAK2 IC_{50} (nM) at 1 mM ATP
42	+	++++
43	+++	++++
44	++	++++
45	++++	++++
46	+++	++++
47	+	+++
48	++	++++
49	+	+++
50	+	+++
51	+	+++
52	+	+++
53	+	+++
54	+	+++
55	+	+++
56	+	+++
57	+	++
58	+	++
59	+	+++

Example	JAK1 IC_{50} (nM) at 1 mM ATP	JAK2 IC_{50} (nM) at 1 mM ATP
60	+	+++
61	+	+
62	+	+
63	+	+++
64	+	+++
65	+	+++
66	+	+++
67	+	+++
68	+	++
69	+	+++
70	+	+
71	+	+++
72	+	++
73	+	++
74	+	++
75	+	++
76	+	++
77	+	+++
78	+	+++
79	+++	++++
80	+	+++
81	+	+++
82	++	++++
83	+	+++
84	+++	++++
85	+	+++
86	++	+++
87	++	++++

Example	JAK1 IC_{50} (nM) at 1 mM ATP	JAK2 IC_{50} (nM) at 1 mM ATP
88	+	+++
89	+	+++
90	+	++
91	+++	++++
92	+	+++
93	+	+++
94	+	+++
95	+	+++
96	+	+++
97	+	+++
98	+	++++
99	+	+++
100	++	++++
101	+	+++
102	+	+++
103	+	+++
104	++	++++
105	++	+++
106	++	++++
107	++	++++
108	++	++++
109	+	+++
110	+	++++
111	++	++++
112	++	+++
113	+	++++
114	+	++++
115	+	++++

Example	JAK1 IC_{50} (nM) at 1 mM ATP	JAK2 IC_{50} (nM) at 1 mM ATP
116	+++	++++
117	+++	++++
118	++	+++
119	+	++
120	+	+++
121	+++	++++
122	+	++++
123	+	++++
124	+++	++++
125	+	+++
126	++	++++
127	+	+++
128	+++	++++
129	+	+++
130	+	++++
131	+	+++
132	+	+++
133	+++	++++
134	+	++++
135	++	++++
136	+	+++
137	++	++++
138	++	++++
139	+	++++
140	++	++++
141	+	+
142	++	++++
143	++	+++

Example	JAK1 IC_{50} (nM) at 1 mM ATP	JAK2 IC_{50} (nM) at 1 mM ATP
144	++	++++
145	++	++++
146	++	++++
147	++	+++
148	++	++++
149	+++	++++
150	++	++++
151	+	+++
152	+	++++
153	+	+++
154	+	+++
155	+	+++
156	+	+++
157	+	+++
158	+	+++
159	+	+++
160	++	++++
161	+	+++
162	+	++++
163	+	+++
164, peak 1	++	++++
164, peak 2	+++	++++
165, peak 1	+++	++++
165, peak 2	+	+++

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 72h. 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.

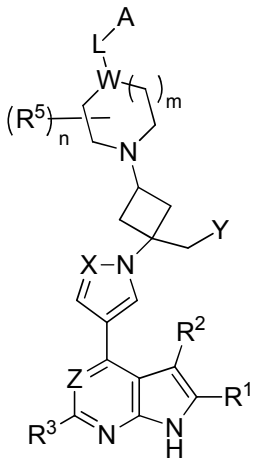
Example G: In vivo protection of bone

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.

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof; wherein:

X is CH or N;

Y is H, cyano, halo, C_{1-3} alkyl, or C_{1-3} haloalkyl;

Z is CR^4 or N;

W is CH or N;

when W is CH, then L is O, S, $C(R^6)_2$, C(=O), $C(=O)N(R^7)$, C(=O)O, $C(=O)C(R^6)_2$, S(=O), $S(=O)_2$, $S(=O)N(R^7)$, $S(=O)_2N(R^7)$, or $C(=NR^{7a})N(R^7)$; or

when W is N, then L is $C(R^6)_2$, C(=O), C(=O)O, $C(=O)N(R^7)$, $C(=O)C(R^6)_2$, S(=O), $S(=O)_2$, $S(=O)N(R^7)$, $S(=O)_2N(R^7)$, or $C(=NR^{7a})N(R^7)$;

R^1, R^2, R^3, and R^4 are each independently H, hydroxy, halo, C_{1-3} alkyl, or C_{1-3} haloalkyl;

each R^5 is independently hydroxy, C_{1-4} alkoxy, fluorine, C_{1-4} alkyl, hydroxy-C_{1-4}-alkyl, C_{1-4} alkoxy-C_{1-4}-alkyl, or C_{1-4} fluoroalkyl;

each R^6 is, independently, H or C_{1-4} alkyl; or

two R^6 groups, together with the carbon atom to which they are attached, form a 3-, 4-, 5-, or 6-membered cycloalkyl ring;

R^7 is H or C_{1-4} alkyl;

R^{7a} is H, OH, CN, C_{1-4} alkoxy, or C_{1-4} alkyl;

or R^7 and R^{7a}, taken together with the C(=N)N moiety to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocycloalkyl ring or a 5- or 6-membered heteroaryl ring;

A is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocycloalkyl, C_{6-10} aryl, or C_{1-10} heteroaryl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocycloalkyl, C_{6-10} aryl, and C_{1-10} heteroaryl are each optionally substituted with p independently selected R^8 substituents; wherein p is 1, 2, 3, 4, or 5; provided when L is O, S, C(=O), C(=O)O, S(=O), or $S(=O)_2$, then A is not H;

each R^8 is independently selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, C_{1-10} heteroaryl-C_{1-4}-alkyl, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^eR^f$, $-C(=O)R^b$, $-C(=O)OR^a$, $-C(=O)NR^eR^f$, $-OC(=O)R^b$, $-OC(=O)NR^eR^f$, $-NR^eR^f$, $-NR^cC(=O)R^d$, $-NR^cC(=O)OR^d$, $-NR^cS(=O)_2R^d$, and $-NR^cS(=O)_2NR^eR^f$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^a, R^c, R^d, R^e, and R^f is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^b is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^g is independently selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, C_{1-7} heteroaryl-C_{1-3}-alkyl,

$-OR^{a1}$, $-SR^{a1}$, $-S(=O)R^{b1}$, $-S(=O)_2R^{b1}$, $-S(=O)_2NR^{e1}R^{f1}$, $-C(=O)R^{b1}$, $-C(=O)OR^{a1}$, $-C(=O)NR^{e1}R^{f1}$, $-OC(=O)R^{b1}$, $-OC(=O)NR^{e1}R^{f1}$, $-NR^{e1}R^{f1}$, $-NR^{c1}C(=O)R^{d1}$, $-NR^{c1}C(=O)OR^{d1}$, - $-NR^{c1}S(=O)_2R^{d1}$, and $-NR^{c1}S(=O)_2NR^{e1}R^{f1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl are each optionally substituted with 1, 2, 3, or 4 independently selected R^h groups;

each R^{a1}, R^{c1}, R^{d1}, R^{e1}, and R^{f1} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^h groups;

each R^{b1} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^h groups;

each R^h is independently selected from cyano, halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino, di-C_{1-4}-alkylamino, hydroxy-C_{1-4} alkyl, C_{1-4} alkoxy-C_{1-4} alkyl, cyano-C_{1-4} alkyl, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino;

m is 0, 1, or 2; and

n is 0, 1, 2, 3, or 4.

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

X is CH or N;

Y is H, cyano, halo, C_{1-3} alkyl, or C_{1-3} haloalkyl;

Z is CR^4 or N;

W is CH or N;

when W is CH, then L is O, S, $C(R^6)_2$, C(=O), $C(=O)N(R^7)$, C(=O)O, $C(=O)C(R^6)_2$, S(=O), $S(=O)_2$, $S(=O)N(R^7)$, or $S(=O)_2N(R^7)$; or

when W is N, then L is $C(R^6)_2$, C(=O), C(=O)O, $C(=O)N(R^7)$, $C(=O)C(R^6)_2$, S(=O), $S(=O)_2$, $S(=O)N(R^7)$, or $S(=O)_2N(R^7)$;

R^1, R^2, R^3, and R^4 are each independently H, hydroxy, halo, C_{1-3} alkyl, or C_{1-3} haloalkyl;

each R^5 is independently hydroxy, C_{1-4} alkoxy, fluorine, C_{1-4} alkyl, hydroxy-C_{1-4}-alkyl, C_{1-4} alkoxy-C_{1-4}-alkyl, or C_{1-4} fluoroalkyl;

each R^6 is, independently, H or C_{1-4} alkyl; or

two R^6 groups, together with the carbon atom to which they are attached, form a 3-, 4-, 5-, or 6-membered cycloalkyl ring;

R^7 is H or C_{1-4} alkyl;

A is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocycloalkyl, C_{6-10} aryl, or C_{1-10} heteroaryl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocycloalkyl, C_{6-10} aryl, and C_{1-10} heteroaryl are each optionally substituted with p independently selected R^8 substituents; wherein p is 1, 2, 3, 4, or 5;

each R^8 is independently selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, C_{1-10} heteroaryl-C_{1-4}-alkyl, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^eR^f$, $-C(=O)R^b$, $-C(=O)OR^a$, $-C(=O)NR^eR^f$, $-OC(=O)R^b$, $-OC(=O)NR^eR^f$, $-NR^eR^f$, $-NR^cC(=O)R^d$, $-NR^cC(=O)OR^d$, $-NR^cS(=O)_2R^d$, and $-NR^cS(=O)_2NR^eR^f$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^a, R^c, R^d, R^e, and R^f is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^b is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl-C_{1-4}-alkyl, C_{2-10} heterocycloalkyl, C_{2-10} heterocycloalkyl-C_{1-4}-alkyl, C_{6-10} aryl, C_{6-10} aryl-C_{1-4}-alkyl, C_{1-10} heteroaryl, and C_{1-10} heteroaryl-C_{1-4}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^g is independently selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, C_{1-7} heteroaryl-C_{1-3}-alkyl, $-OR^{a1}$, $-SR^{a1}$, $-S(=O)R^{b1}$, $-S(=O)_2R^{b1}$, $-S(=O)_2NR^{e1}R^{f1}$, $-C(=O)R^{b1}$, $-C(=O)OR^{a1}$, $-C(=O)NR^{e1}R^{f1}$, $-OC(=O)R^{b1}$, $-OC(=O)NR^{e1}R^{f1}$, $-NR^{e1}R^{f1}$, $-NR^{c1}C(=O)R^{d1}$, $-NR^{c1}C(=O)OR^{d1}$, - $-NR^{c1}S(=O)_2R^{d1}$, and $-NR^{c1}S(=O)_2NR^{e1}R^{f1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl are each optionally substituted with 1, 2, 3, or 4 independently selected R^h groups;

each R^{a1}, R^{c1}, R^{d1}, R^{e1}, and R^{f1} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^h groups;

each R^{b1} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-3}-alkyl, C_{2-7} heterocycloalkyl, C_{2-7} heterocycloalkyl-C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-7} heteroaryl, and C_{1-7} heteroaryl-C_{1-3}-alkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^h groups;

each R^h is independently selected from cyano, halo, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino, di-C_{1-4}-alkylamino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino;

m is 0, 1, or 2; and

n is 0, 1, 2, 3, or 4.

3. The compound of either claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein X is N.

4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein Z is N.

5. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein Z is CH.

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

7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein L is $C(R^6)_2$, C(=O), C(=O)O, $C(=O)N(R^7)$, $S(=O)_2$, $S(=O)_2N(R^7)$ or $C(=NR^{7a})N(R^7)$.

8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein R^6 is H, R^7 is H or methyl, and R^{7a} is CN.

9. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein W is CH.

10. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein L is O.

11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein Y is cyano.

12. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, and R^4 are each H.

13. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein n is 0.

14. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein m is 1.

15. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein A is H, methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, 1,2-dimethylpropyl, 1-(tert-butyl)methyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, a tetrahydropyran ring, a pyrrolidine ring, a piperidine ring, a pyridine ring, a pyrimidine ring, a thiazole ring, or a pyrazine ring; each of which is optionally substituted with p independently selected R^8 substituents; provided when L is O, S, C(=O), C(=O)O, S(=O), or $S(=O)_2$, then A is not H.

16. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein each R^8 is independently selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^eR^f$, $-C(=O)R^b$, $-C(=O)OR^a$, $-C(=O)NR^eR^f$, $-OC(=O)R^b$, $-OC(=O)NR^eR^f$, $-NR^eR^f$, $-NR^cC(=O)R^d$, $-NR^cC(=O)OR^d$, $-NR^cS(=O)_2R^d$, and $-NR^cS(=O)_2NR^eR^f$; wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^g groups.

17. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein each R^8 is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{2-7} heterocycloalkyl, $-OR^a$, $-C(=O)OR^a$, or $-NR^eR^f$; wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^g groups; and wherein each R^a, R^e, and R^f is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl.

18. The compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein each R^g is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{2-7} heterocycloalkyl, $-OR^{a1}$, $-S(=O)_2R^{b1}$, $-S(=O)_2NR^{e1}R^{f1}$, $-C(=O)R^{b1}$, $-C(=O)OR^{a1}$, and $-NR^{e1}R^{f1}$; wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-7} heterocycloalkyl and are each optionally substituted by 1, 2, 3, or 4 independently selected R^h groups.

19. The compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, wherein each R^g is independently selected from C_{2-7} heterocycloalkyl, $-OR^{a1}$, $-NR^{e1}R^{f1}$; wherein said C_{2-7} heterocycloalkyl is optionally substituted by 1 or 2 R^h groups independently selected from fluoro, OH, C_{1-3} alkyl, C_{1-3} alkoxy, and hydroxy-C_{1-4} alkyl; and wherein each R^{a1}, R^{e1} and R^{f1} are independently selected from H, C_{3-7} cycloalkyl, and C_{1-6} alkyl.

20. The compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein each R^h is independently selected from fluoro, OH, C_{1-3} alkyl, C_{1-3} alkoxy, and hydroxy-C_{1-4} alkyl.

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

X is N;

Z is N;

R^1, R^2, and R^3 are each H;

Y is cyano;

W is N and L is $C(R^6)_2$, C(=O), C(=O)N(R^7), $S(=O)_2$, or $S(=O)_2N(R^7)$; or

W is CH and L is O;

A is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocycloalkyl, C_{6-10} aryl, or C_{1-10} heteroaryl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocycloalkyl, C_{6-10} aryl, and C_{1-10} heteroaryl are each optionally substituted with p independently selected R^8 substituents; wherein p is 1, 2, 3, 4, or 5;

each R^8 is independently selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^eR^f$, $-C(=O)R^b$, $-C(=O)OR^a$, $-C(=O)NR^eR^f$, $-OC(=O)R^b$, $-OC(=O)NR^eR^f$, $-NR^eR^f$, $-NR^cC(=O)R^d$, $-NR^cC(=O)OR^d$, $-NR^cS(=O)_2R^d$, and $-NR^cS(=O)_2NR^eR^f$; wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^g is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{2-7} heterocycloalkyl, $-OR^{a1}$, $-S(=O)_2R^{b1}$, $-S(=O)_2NR^{e1}R^{f1}$, $-C(=O)R^{b1}$, $-C(=O)OR^{a1}$, and $-NR^{e1}R^{f1}$; wherein said C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-7} heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^h groups;

each R^a, R^c, R^d, R^e, and R^f is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^b is independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

each R^{a1}, R^{c1}, R^{d1}, R^{e1}, and R^{f1} is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^{b1} is independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl;

n is 0; and

m is 1.

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

X is N;

Z is N;

R^1, R^2, and R^3 are each H;

Y is cyano;

W is N and L is $C(R^6)_2$, C(=O), C(=O)N(R^7), $S(=O)_2$, or $S(=O)_2N(R^7)$; or

W is CH and L is O;

A is C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocycloalkyl, C_{6-10} aryl, or C_{1-10} heteroaryl; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-10} heterocycloalkyl, C_{6-10} aryl, and C_{1-10} heteroaryl are each optionally substituted with p independently selected R^8 substituents; wherein p is 1, 2, 3, 4, or 5;

each R^8 is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, -OR^a, or -NR^eR^f; wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^g is independently selected from C_{2-7} heterocycloalkyl and -$NR^{e1}R^{f1}$; wherein said C_{2-7} heterocycloalkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^h groups;

each R^h is independently selected from C_{1-4} alkyl;

each R^a, R^e, and R^f is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^{a1}, R^{e1}, and R^{f1} is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

n is 0; and

m is 1.

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

X is N;

Z is N;

R^1, R^2, and R^3 are each H;

Y is cyano;

W is N and L is $C(R^6)_2$, C(=O), C(=O)N(R^7), $S(=O)_2$, or $S(=O)_2N(R^7)$;

R^6 is H;

R^7 is H or methyl;

A is methyl, ethyl, cyclopropyl, phenyl, a pyrrolidine ring, a piperidine ring, a pyridine ring, a pyrimidine ring, a thiazole ring, or a pyrazine ring; each of which is optionally substituted with p independently selected R^8 substituents; wherein p is 1, 2, or 3;

each R^8 is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, or $-NR^eR^f$; wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^g groups;

each R^g is independently selected from C_{2-7} heterocycloalkyl and $-NR^{e1}R^{f1}$; wherein said C_{2-7} heterocycloalkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^h groups;

each R^h is independently C_{1-4} alkyl;

each R^a, R^e, and R^f is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^{a1}, R^{e1}, and R^{f1} is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

n is 0; and

m is 1.

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

X is N;

Z is N;

R^1, R^2, and R^3 are each H;

Y is cyano;

W is CH and L is O;

R^6 is H;

R^7 is H or methyl;

A is phenyl, which is optionally substituted with p independently selected R^8 substituents; wherein p is 1, 2, or 3;

each R^8 is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^a$, or $-NR^eR^f$; wherein said C_{1-6} alkyl is optionally substituted by p independently selected R^g groups;

each R^g is independently selected from C_{2-7} heterocycloalkyl and $-NR^{e1}R^{f1}$; wherein said C_{2-7} heterocycloalkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^h groups;

each R^h is independently C_{1-4} alkyl;

each R^a, R^e, and R^f is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^{a1}, R^{e1}, and R^{f1} is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

n is 0; and

m is 1.

25. The compound of to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

X is N;

Z is N;

R^1, R^2, and R^3 are each H;

Y is cyano;

W is N and L is $C(R^6)_2$, C(=O), C(=O)O, $C(=O)N(R^7)$, $S(=O)_2$, $S(=O)_2N(R^7)$ or $C(=NR^{7a})N(R^7)$; or

W is CH and L is O;

R^6 is H;

R^7 is H or methyl;

R^{7a} is CN;

A is H, methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, 1,2-dimethylpropyl, 1-(tert-butyl)methyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, a tetrahydropyran ring, a pyrrolidine ring, a piperidine ring, a pyridine ring, a pyrimidine ring, a thiazole ring, or a pyrazine ring; wherein said methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, 1,2-dimethylpropyl, 1-(tert-butyl)methyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, a tetrahydropyran ring, pyrrolidine ring, piperidine ring, pyridine ring, pyrimidine ring, thiazole ring, and pyrazine ring are each optionally substituted with p independently selected R^8 substituents; provided when L is O, S, C(=O), C(=O)O, S(=O), or $S(=O)_2$, then A is not H;

each R^8 is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{2-7} heterocycloalkyl, $-OR^a$, $-C(=O)OR^a$, or $-NR^eR^f$; wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^g groups; and wherein each R^a, R^e, and R^f is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^g is independently selected from C_{2-7} heterocycloalkyl, $-OR^{a1}$, $-NR^{e1}R^{f1}$; wherein said C_{2-7} heterocycloalkyl is optionally substituted by 1 or 2 R^h groups independently selected from fluoro, OH, C_{1-3} alkyl, C_{1-3} alkoxy, and hydroxy-C_{1-4} alkyl; and wherein each R^{a1}, R^{e1} and R^{f1} are independently selected from H, C_{3-7} cycloalkyl, and C_{1-6} alkyl;

p is 1, 2, or 3;

m is 1; and

n is 0.

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

X is N;

Z is N;

R^1, R^2, and R^3 are each H;

Y is cyano;

W is N and L is $C(R^6)_2$, C(=O), C(=O)O, $C(=O)N(R^7)$, $S(=O)_2$, or $S(=O)_2N(R^7)$; or

W is CH and L is O;

R^6 is H;

R^7 is H or methyl;

A is methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, 1,2-dimethylpropyl, 1-(tert-butyl)methyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, a tetrahydropyran ring, a pyrrolidine ring, a piperidine ring, a pyridine ring, a pyrimidine ring, a thiazole ring, or a pyrazine ring; each of which is optionally substituted with p independently selected R^8 substituents;

each R^8 is independently selected from halo, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, C_{2-7} heterocycloalkyl, $-OR^a$, $-C(=O)OR^a$, or $-NR^eR^f$; wherein said C_{1-6} alkyl is optionally substituted by 1, 2, 3, or 4 independently selected R^g groups; and wherein each R^a, R^e, and R^f is independently selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl;

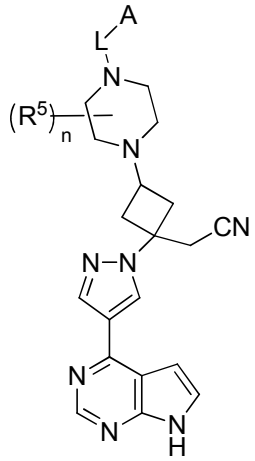
each R^g is independently selected from C_{2-7} heterocycloalkyl, $-OR^{a1}$, $-NR^{e1}R^{f1}$; wherein said C_{2-7} heterocycloalkyl is optionally substituted by 1 or 2 R^h groups independently selected from fluoro, OH, C_{1-3} alkyl, C_{1-3} alkoxy, and hydroxy-C_{1-4} alkyl; and wherein each R^{a1}, R^{e1} and R^{f1} are independently selected from H, C_{3-7} cycloalkyl, and C_{1-6} alkyl;

p is 1, 2, or 3;

m is 1; and

n is 0.

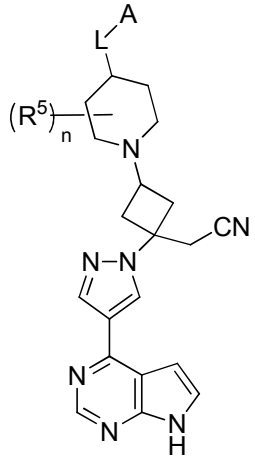
27. The compound of any one of claims 1-2, 21-23, and 25-26, wherein said compound has Formula IV:



IV

or a pharmaceutically acceptable salt thereof.

28. The compound of any one of claims 1-2, 21-22, and 24-26, wherein said compound has Formula V:



V

or a pharmaceutically acceptable salt thereof.

29. The compound of claim 1, selected from:

3-[(4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)methyl]-5-fluorobenzonitrile;

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

yl]cyclobutyl}piperazin-1-yl)methyl]-6-(dimethylamino)-2-fluorobenzonitrile;

4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[4-fluoro-2-(trifluoromethyl)phenyl]piperazine-1-carboxamide;

{3-(4-{[(2S)-2-methylpyrrolidin-1-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-(4-{[(2S)-2-ethylpyrrolidin-1-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[3-fluoro-2-(trifluoromethyl)isonicotinoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

[1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile;

{3-[4-(3,5-difluorobenzoyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[(2-chloro-5-fluoropyridin-3-yl)carbonyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[(5-fluoropyridin-3-yl)carbonyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[2-(difluoromethyl)-3-fluoroisonicotinoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

3-[(4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)carbonyl]-5-fluorobenzonitrile;

[1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile;

[1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[6-(trifluoromethyl)pyrazin-2-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile;

{3-[4-(3,4-difluorobenzoyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-[4-(2-chloro-3,6-difluorobenzyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[3-fluoro-5-(trifluoromethyl)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-

d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[2-fluoro-4-(trifluoromethyl)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-[4-(pyrrolidin-1-ylcarbonyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)cyclobutyl}acetonitrile;

{3-(4-{[6-(difluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[2-fluoro-3-(trifluoromethyl)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[(5-fluoropyridin-3-yl)methyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[(2-isopropylpyrimidin-4-yl)carbonyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-[4-(piperidin-1-ylcarbonyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[4-fluoro-3-(trifluoromethoxy)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-(4-{[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[4-chlorobenzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-{4-[2-fluoro-4-(trifluoromethyl)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N,N-dimethylpiperazine-1-carboxamide;

{3-(4-{3-[(dimethylamino)methyl]-5-fluorobenzoyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-(4-{3-[(dimethylamino)methyl]-5-fluorobenzyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-

d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-[4-(ethylsulfonyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-[4-(cyclopropylsulfonyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N,N-dimethylpiperazine-1-sulfonamide;

4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-ethyl-N-methylpiperazine-1-carboxamide;

{3-{4-[3-[(dimethylamino)methyl]-5-(trifluoromethyl)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-[4-(3-fluoro-5-{[(2S)-2-methylpyrrolidin-1-yl]methyl}phenoxy)piperidin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{3-(4-{3-[(dimethylamino)methyl]-5-fluorophenoxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

[1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile-d1; and

or a pharmaceutically acceptable salt of any of the aforementioned.

30. The compound of claim 1, selected from:

3-[(4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)carbonyl]-5-[(dimethylamino)methyl]benzonitrile;

3-[(4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)methyl]-5-[(dimethylamino)methyl]benzonitrile;

3-[(4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)methyl]-5-[(dimethylamino)methyl]benzonitrile;

{trans-3-{4-[3-[(dimethylamino)methyl]-5-(trifluoromethyl)benzyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-{4-[3-[(dimethylamino)methyl]-5-(trifluoromethyl)benzyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[6-[(ethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

6-[(4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)carbonyl]-2-(trifluoromethyl)pyrimidine-4-carboxylic acid;

{trans-3-(4-{[6-(azetidin-1-ylmethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[6-[(methylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[6-(hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[6-[(dimethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[6-(pyrrolidin-1-ylmethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[6-(aminomethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[6-[(isopropylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[6-[(cyclobutylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[6-[(tert-butylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[6-(1-hydroxy-1-methylethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-(4-{[6-(1-hydroxy-1-methylethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[6-(methoxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[6-(1-aminocyclobutyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-(4-{[6-(1-aminocyclobutyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[6-[1-(dimethylamino)cyclobutyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-(4-{[6-[1-(dimethylamino)cyclobutyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-[(dimethylamino)methyl]-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile ;

{trans-3-(4-{[4-(hydroxymethyl)-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-(aminomethyl)-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-[(methylamino)methyl]-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[6-(1-methoxy-1-methylethyl)-2-(trifluoromethyl)pyrimidin-4-

yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[6-[1-(methylamino)cyclobutyl]-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

2-[(4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)carbonyl]-6-(trifluoromethyl)isonicotinonitrile;

{trans-3-(4-{[6-(1-hydroxycyclobutyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-(4,5-dihydro-1H-imidazol-2-yl)-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{3-(difluoromethyl)-5-[(dimethylamino)methyl]benzoyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-(1-hydroxy-1-methylethyl)-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-(methoxymethyl)-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[6-(1-hydroxy-1-methylethyl)-2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)-1-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-isopropyl-N-methylpiperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-methyl-N-propylpiperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-ethylpiperazine-1-carboxamide;

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

yl]cyclobutyl}-N-[3-(dimethylamino)propyl]-N-methylpiperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-cyclopropyl-N-methylpiperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-methyl-N-(2,2,2-trifluoroethyl)piperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-isopropylpiperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-(trans-4-hydroxycyclohexyl)piperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(3R)-tetrahydrofuran-3-yl]piperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-(2-hydroxycyclopentyl)piperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1S,2R)-2-hydroxycyclopentyl]piperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-cyclopentylpiperazine-1-carboxamide;

{trans-3-(4-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}piperazin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-(cyclopropylmethyl)piperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1R)-1,2-dimethylpropyl]piperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1S)-1,2-dimethylpropyl]piperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1S)-1-cyclopropylethyl]piperazine-1-carboxamide;

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

yl]cyclobutyl}-N-[(1R)-1-cyclopropylethyl]piperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-cyclopropylpiperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-cyclobutylpiperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-(2,2-dimethylpropyl)piperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-isobutylpiperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1R)-1-methylpropyl]piperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1S)-1-methylpropyl]piperazine-1-carboxamide;

4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-cyclobutylpiperazine-1-carboxamide;

4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1R)-1-methylpropyl]piperazine-1-carboxamide;

4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1S)-1-methylpropyl]piperazine-1-carboxamide;

4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-cyclopropylpiperazine-1-carboxamide;

4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-isopropylpiperazine-1-carboxamide;

4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-cyclopentylpiperazine-1-carboxamide;

4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1R)-1,2-dimethylpropyl]piperazine-1-carboxamide;

4-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1S)-1,2-dimethylpropyl]piperazine-1-carboxamide;

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

yl]cyclobutyl}-N-methylpiperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1R)-2,2,2-trifluoro-1-methylethyl]piperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1S)-2,2,2-trifluoro-1-methylethyl]piperazine-1-carboxamide;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[(1S)-1-(trifluoromethyl)propyl]piperazine-1-carboxamide;

[trans-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[(2R)-2-(trifluoromethyl)pyrrolidin-1-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile;

[trans-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[(2S)-2-(trifluoromethyl)pyrrolidin-1-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile;

N'-cyano-4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N,N-dimethylpiperazine-1-carboximidamide;

{trans-3-[4-(methylsulfonyl)piperazin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile ;

isopropyl 4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazine-1-carboxylate;

{cis-3-(4-{[4-(methoxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-(methoxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-(hydroxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-(4-{[4-(hydroxymethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-(1-hydroxy-1-methylethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-[(tert-butylamino)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-(4-{[4-[(tert-butylamino)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-(aminomethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-[(dimethylamino)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-[(ethylamino)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-[(methylamino)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

2-[(1-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperidin-4-yl)oxy]-6-(trifluoromethyl)isonicotinonitrile;

2-[(1-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperidin-4-yl)oxy]-6-(trifluoromethyl)isonicotinonitrile;

{cis-3-{4-[3-[(dimethylamino)methyl]-5-(trifluoromethyl)benzoyl]piperazin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

3-[(4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperazin-1-yl)carbonyl]-5-[(dimethylamino)methyl]benzonitrile;

{cis-3-(4-{[6-(pyrrolidin-1-ylmethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-(4-{[6-(morpholin-4-ylmethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-(4-{[6-(azetidin-1-ylmethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

3-[(1-{cis-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}piperidin-4-yl)oxy]-5-[(dimethylamino)methyl]benzonitrile;

{cis-3-{4-[3-[(dimethylamino)methyl]-5-(trifluoromethyl)phenoxy]piperidin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-{4-[3-[(diethylamino)methyl]-5-(trifluoromethyl)phenoxy]piperidin-1-yl}-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-(4-{3-(difluoromethyl)-5-[(dimethylamino)methyl]phenoxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-[4-({6-chloro-4-[(dimethylamino)methyl]pyridin-2-yl}oxy)piperidin-1-yl]-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-(4-{[6-[(dimethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-(4-{[6-[(ethylamino)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-(4-{[6-[(3-hydroxyazetidin-1-yl)methyl]-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-(4-{[6-methyl-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-(4-{[6-(hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-(4-{[6-(aminomethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

4-{trans-3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}-N-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]piperazine-1-carboxamide;

{trans-3-(4-{[4-{[(2-hydroxy-1,1-dimethylethyl)amino]methyl}-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-{[(2-hydroxyethyl)amino]methyl}-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-{[(3-hydroxypropyl)amino]methyl}-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-(azetidin-1-ylmethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-[(3-hydroxyazetidin-1-yl)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-(pyrrolidin-1-ylmethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-(morpholin-4-ylmethyl)-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-[(3,3-difluoropyrrolidin-1-yl)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-{[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl}-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-{[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]methyl}-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[4-(1-hydroxy-1-methylethyl)-6-(trifluoromethyl)pyridin-2-yl]carbonyl}piperazin-1-yl)-1-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-(4-{[6-(2-hydroxyethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{trans-3-(4-{[6-(2-hydroxyethyl)-2-(trifluoromethyl)pyrimidin-4-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

{cis-3-(4-{[4-[(2-oxo-1,3-oxazolidin-3-yl)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile; and

{trans-3-(4-{[4-[(2-oxo-1,3-oxazolidin-3-yl)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile;

or a pharmaceutically acceptable salt of any of the aforementioned.

31. The compound of any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, wherein the cyclobutyl ring in Formula I is the *cis* form.

32. The compound of any one of claims 1 to 29, or a pharmaceutically acceptable salt thereof, wherein the cyclobutyl ring in Formula I is the *trans* form.

33. The compound of claim 1, wherein the compound is *trans*-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]-3-(4-{[2-(trifluoromethyl)pyrimidin-4-yl]carbonyl}piperazin-1-yl)cyclobutyl]acetonitrile, or a pharmaceutically acceptable salt thereof.

34. The compound of claim 1, wherein the compound is {*trans*-3-(4-{[4-[(3-hydroxyazetidin-1-yl)methyl]-6-(trifluoromethyl)pyridin-2-yl]oxy}piperidin-1-yl)-1-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]cyclobutyl}acetonitrile, or a pharmaceutically acceptable salt thereof.

35. A composition comprising a compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

36. A composition comprising a compound of claim 33, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

37. A composition comprising a compound of claim 34, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

38. Use of a compound according to any one of claims 1 to 34, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for inhibiting an activity of JAK1

39. The use of 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 34, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the 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 of 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 of claim 40, wherein said autoimmune disease is rheumatoid arthritis.

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

44. The use of 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 of claim 40, wherein said cancer is a solid tumor.

46. The use of 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 of claim 40, wherein said cancer is lymphoma, leukemia, or multiple myeloma.

48. The use of claim 40, wherein said myeloproliferative disorder (MPD) is polycythemia vera (PV), essential thrombocythemia (ET), myeloid metaplasia with myelofibrosis (MMM), 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 of claim 40, wherein said myeloproliferative disorder is myelofibrosis.

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

51. The use of 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.