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(54) Title: GEMINALLY SUBSTITUTED CYANOETHYLPYRAZOLO PYRIDONES AS JANUS KINASE INHIBITORS

(57) Abstract: Disclosed are geminally substituted cyanoethylpyrazolo pyridones as Janus Kinase inhibitors, which are useful in the treatment of iJAK-mediated diseases such as rheumatoid arthritis, asthma, COPD and cancer.

GEMINALLY SUBSTITUTED CYANOETHYLPYRAZOLO PYRIDONES AS JANUS KINASE INHIBITORS

BACKGROUND OF THE INVENTION

Protein kinases are a group of enzymes that regulate the activity of their target proteins by the addition of phosphate groups to the protein substrate. Kinases play an essential role in many physiological processes including cell division, differentiation, cellular homeostasis and signal transduction. Kinases can be subdivided by their target into Serine/Threonine kinases and Tyrosine kinases. Tyrosine kinases are further subdivided into receptor tyrosine kinases and non-receptor tyrosine kinases. The mammalian Janus kinase (JAK) family members are non-receptor tyrosine kinases.

The JAK family has four members; JAK1, JAK2, JAK3 and TYK2. JAK1, JAK2 and TYK2 are universally expressed, whereas JAK3 expression is limited to hematopoetic cells. The JAK family is involved in intracellular signal transduction from >70 different cytokines. Cytokines bind to their cell surface receptors resulting in receptor dimerization and subsequent activation/phosphorylation of JAK tyrosine kinases. The JAKs are either constitutively associated with the receptor or are recruited upon cytokine binding. Specific tyrosine residues on the receptor are then phosphorylated by activated JAKs and serve as docking sites for STAT proteins. STATs are phosphorylated by JAKs, dimerize, then translocate to the nucleus where they bind specific DNA elements and activate gene transcription. JAK1 signals in conjunction with all JAK isoforms in a cytokine dependent manner.

JAKs are essential for multiple physiological functions. This has been demonstrated using genetically engineered mouse models that are deficient in specific JAKs. $Jak1^{-/-}$ mice die perinatally, while $Jak2^{-/-}$ mice have deficiencies in erythropoesis and die around day E12. $Jak3^{-/-}$ mice are viable, but have a SCID phenotype with deficiencies in T cells, B cells and NK cells. $TYK2^{-/-}$ mice exhibit features of hyper IgE syndrome. These phenotypes demonstrate the essential and non-redundant roles of JAK activity in vivo (K. Ghoreschi, A. Laurence, J. J. O'Shea, *Immunol. Rev.* 228, 273 (2009)).

Furthermore, mutations in the JAK enzymes have been associated with diseases in humans. Inactivating mutations in JAK3 (or the cognate common gamma chain cytokine receptor) cause a severe SCID phenotype (J. J. O'Shea, M. Pesu, D. C. Borie, P. S. Changelian, *Nat. Rev. Drug Discov.* 3, 555 (2004)). Deletions of TYK2 result in hyper IgG syndrome and increased infection risk (Y. Minegishi *et al.*, *Immunity.* 25, 745 (2006)). No inactivating mutations have been reported for JAK1 or JAK2, consistent with the data from mice that demonstrates that JAK1 and JAK2 deficient mice are not viable. However, several mutations that result in constitutively active JAK2 have been identified, resulting in myeloproliferative diseases and confirming the central role of JAK2 in hematopoesis (O. bdel-Wahab, *Curr. Opin. Hematol.* 18, 117 (2011)). JAK2 is the sole JAK family member involved in signal transduction of the critical hematopoetic cytokines IL-3, GMCSF, EPO and TPO.

The wealth of mouse and human genetic data demonstrating a central role for JAK kinase activity in autoimmune disease, hematopoesis and oncology has been supported by the use of pan-JAK inhibitors in clinical trials for autoimmune diseases and neoplasms (See K. Ghoreschi, et al, *Immunol. Rev.* 228, 273 (2009), *and* A. Quintas-Cardama, H. Kantarjian, J. Cortes, S. Verstovsek, *Nat. Rev. Drug Discov.* 10, 127 (2011)).

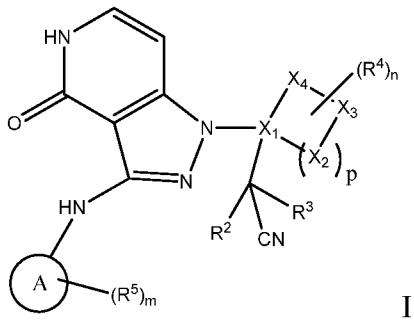
A considerable body of literature has accumulated that link the Jak/STAT pathway to various diseases and disorders including hyperproliferative disorders and cancer such as leukemia and lymphomas, immunological and inflammatory disorders such as transplant rejection, asthma, chronic obstructive pulmonary disease, allergies, rheumatoid arthritis, type I diabetes, amyotropic lateral sclerosis and multiple sclerosis.

SUMMARY OF THE INVENTION

The present invention provides novel compounds which are inhibitors of JAKs. The invention also provides a method for the treatment and prevention of JAK-mediated diseases and disorders using the novel compounds, as well as pharmaceutical compositions containing the compounds.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds of formula I or pharmaceutically acceptable salts, or stereoisomers thereof:



I

A is selected from aryl, heteroaryl, cycloalkyl$C_{(0-10)}$alkyl, C_{1-6}alkyl;

R^2 and R^3 are each independently selected from hydrogen, C_{1-4}alkyl and hydroxyl, wherein R^2 and R^3 may optionally, join together with the carbon they are attached to to form a 3 to 6 membered ring;

X_1, X_2, X_3, and X_4 are each independently selected from O, N, S, and C and provided that the formed ring system contains 0, 1, 2, or 3 atoms selected from O, N and S;

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

m is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3, or 4;

R^4 is selected from:

halogen,

oxo (=O),

C_{1-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{1-10} heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{2-10} alkenyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

aryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{3-8} cycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

(C_{3-8})heterocycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,

C_{0-10} alkylamino(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

(C_{1-10})heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10}alkyl,

(C_{1-10})heteroalkylamino(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$alkyl,

C_{3-8} cycloalkyl C_{0-10} alkylaminoC_{0-10} alkyl,

aryl C_{0-10} alkylaminoC_{0-10} alkyl,

heteroaryl C_{0-10} alkylaminoC_{0-10} alkyl,

(C_{3-8})heterocycloalkyl C_{0-10} alkylaminoC_{0-10} alkyl,

C_{1-10} alkylsulfonyl,

C_{1-10} heteroalkylsulfonyl,

(C_{3-8})cycloalkylC_{0-10}alkylsulfonyl,

(C_{3-8})cycloheteroalkylC_{0-10}alkylsulfonyl,

heteroarylC_{0-10} alkylsulfonyl,

arylC_{0-10} alkylsulfonyl,

$-SO_2NH_2$,

$-SO_2NH(C_{1-6}alkyl)$,

$-SO_2N(C_{1-6}alkyl)_2$,

C_{0-10} alkylsulfamoyl,

C_{1-10} heteroalkylsulfamoyl,

(C_{3-8})cycloalkylC_{0-10} alkylsulfamoyl,

(C_{3-8})cycloheteroalkylC_{0-10} alkylsulfamoyl,

heteroarylC_{0-10} alkylsulfamoyl,

arylC_{0-10} alkylsulfamoyl,

$(C_{0-10}$ alkyl$)_{1-2}$ amino,

$-CO_2(C_{0-10}$ alkyl),

$-(C_{0-10}$ alkyl$)CO_2H$,

$-SO_2CF_3$,

$-SO_2CF_2H$,

C_{1-10} alkylsulfinyl,

C_{1-4}acylaminoC_{0-10} alkyl,

hydroxy,

$-(C_{1-10}$ alkyl$)OH$,

$-C_{0-10}$ alkylalkoxy,

cyano,

$(C_{1-6}$alkyl)cyano, and

C_{1-6}haloalkyl,

wherein two R^4 together with the atoms to which they are attached optionally may form a ring;

R^5 is selected from:

halogen,

oxo (=O),

C_{1-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{1-10} heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{2-10} alkenyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

aryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{3-8} cycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

(C_{3-8})heterocycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,

(C_{1-10})heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,

C_{3-8} cycloalkyl C_{0-10} alkylaminoC_{0-10} alkyl,

aryl C_{0-10} alkylaminoC_{0-10} alkyl,

heteroaryl C_{0-10} alkylaminoC_{0-10} alkyl,

(C_{3-8})heterocycloalkyl C_{0-10} alkylaminoC_{0-10} alkyl,

$-SF_5$,

C_{1-10} alkylsulfonyl,

C_{1-10} heteroalkylsulfonyl,

(C_{3-8})cycloalkylC_{0-10}alkylsulfonyl,

(C_{3-8})cycloheteroalkylC_{0-10}alkylsulfonyl,

heteroarylC_{0-10} alkylsulfonyl,

arylC_{0-10} alkylsulfonyl,

C_{0-10} alkylsulfamoyl,

C_{1-10} heteroalkylsulfamoyl,

(C_{3-8})cycloalkylC_{0-10} alkylsulfamoyl,

(C_{3-8})cycloheteroalkylC_{0-10} alkylsulfamoyl,

heteroarylC_{0-10} alkylsulfamoyl,

$-SO_2NH_2$,

$-SO_2NH(C_{1-6}alkyl)$,

$-SO_2N(C_{1-6}alkyl)_2$,

arylC_{0-10} alkylsulfamoyl,

(C_{0-10} alkyl)$_{1-2}$ amino,

$-CO_2(C_{0-10}$ alkyl),

$-(C_{0-10}$ alkyl)CO_2H,

$-SO_2CF_3$,

$-SO_2CF_2H$,

C_{1-10} alkylsulfinyl,

C_{1-4}acylaminoC_{0-10} alkyl,

hydroxy,

$-(C_{1-10}$ alkyl)OH,

C_{0-10} alkylalkoxy,

cyano,

(C_{1-6}alkyl)cyano, and

C_{1-6}haloalkyl; and

wherein R^4 and R^5 are each optionally substituted with 1, 2, 3, or 4 R^6 substituents and R^6 is independently selected from:

halogen,

C_{1-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{1-10} heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{2-10} alkenyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

aryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{3-8} cycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

(C_{3-8})heterocycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{1-10} alkyl(carbonyl)$_{0-1}$oxyC_{0-10} alkyl,

C_{2-10} alkenyl(carbonyl)$_{0-1}$oxyC_{0-10} alkyl,

C_{1-10} heteroalkyl(carbonyl)$_{0-1}$oxyC_{0-10} alkyl,

aryl C_{0-10} alkyl (carbonyl)$_{0-1}$oxyC_{0-10} alkyl,

(C_{3-8})cycloalkyl C_{0-10} alkyl(carbonyl)$_{0-1}$oxyC_{0-10} alkyl,

heteroarylC_{0-10} alkyl(carbonyl)$_{0-1}$oxyC_{0-10} alkyl,

(C_{3-8})heterocycloalkyl C_{0-10} alkyl(carbonyl)$_{0-1}$oxyC_{0-10} alkyl,

((C_{0-10})alkyl)$_{1-2}$aminocarbonyloxy,

aryl (C_{0-10})alkylaminocarbonyloxy,

-CO_2(C_{0-10} alkyl),

-(C_{0-10} alkyl)CO_2H,

oxo (=O),

C_{1-10} alkylsulfonyl,

C_{1-10} heteroalkylsulfonyl,

(C_{3-8}) cycloalkylsulfonyl,

(C_{3-8}) cycloheteroalkylsulfonyl,

heteroarylsulfonyl,

arylsulfonyl,

aminosulfonyl,

$-SO_2NH_2$,

$-SO_2NH(C_{1-6}alkyl)$,

$-SO_2N(C_{1-6}alkyl)_2$,

$-SO_2CF_3$,

$-SO_2CF_2H$,

C_{1-10} alkylsulfinyl,

amino,

$(C_{0-10}$ alkyl$)_{1-2}$ amino,

$-(oxy)_{0-1}(carbonyl)_{0-1}N(C_{0-10}$ alkyl$)_{1-2}$

C_{1-4}acylaminoC_{0-10} alkyl,

hydroxy,

$(C_{1-10}$ alkyl$)OH$,

C_{1-10} alkoxy,

$(C_{1-10}$ alkyl$)$cyano,

cyano, and

C_{1-6}haloalkyl; and

R^6 is optionally substituted with 1, 2, or 3 substituents selected from hydrogen, hydroxy, (C_{1-6})alkyl, (C_{1-6})alkoxy, $(C_{1-10}$ alkyl$)OH$, halogen, CO_2H, $-(C_{0-6})$alkylCN, $-O(C=O)C_1$-C_6 alkyl, NO_2, trifluoromethoxy, trifluoroethoxy, trifluoromethyl, trifluoroethyl, $-N$-$C(O)O(C_{0-6})$alkyl, C_{1-10} alkylsulfonyl, oxo (O=), aminosulfonyl, $-SO_2C_{1-6}$alkyl, $-SO_2CF_3$, $-SO_2CF_2H$, $-C_{1-10}$ alkylsulfinyl, $-O_{(0-1)}(C_{1-10})$halo, $-SO_2NH_2$, $-SO_2NH(C_{1-6}alkyl)$, $-SO_2N(C_{1-6}alkyl)_2$, alkyl, amino$(C_{1-6}alkyl)_{0-2}$ and NH_2.

Representative compounds of the instant invention include, but are not limited to the following compounds and their pharmaceutically acceptable salts and stereoisomers thereof:

tert-butyl 3-(cyanomethyl)-3-(4-oxo-3-(phenylamino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)azetidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(4-oxo-3-(phenylamino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-[3-(ethylamino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-{3-[(cyclopropylmethyl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-[3-(cyclobutylamino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate;

tert-butyl 3-(cyanomethyl)-3-[3-(ethylamino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]azetidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-[3-(methylamino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate;

tert-butyl 3-(cyanomethyl)-3-[3-(cyclopropylamino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]azetidine-1-carboxylate;

tert-butyl 3-(cyanomethyl)-3-(4-oxo-3-((2-(trifluoromethyl)pyridin-4-yl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)azetidine-1-carboxylate;

tert-butyl 3-(cyanomethyl)-3-(3((4(methoxycarbonyl)phenyl) amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)azetidine-1-carboxylate;

tert-butyl 3-(cyanomethyl)-3-(3-((4-fluorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)azetidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-[4-oxo-3-({4-[2,2,2-trifluoro-hydroxyethyl]phenyl}amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-{4-oxo-3-[(4-sulfamoylphenyl)amino]-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(4-oxo-3-{[1-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-isoindol-5-yl]amino}-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-3-fluoro-4-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-{3-[(2-methyl-1,1-dioxido-2,3-dihydro-1,2-benzisothiazol-5-yl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(4-oxo-3-{[4-(pentafluorosulfanyl)phenyl]amino}-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(4-oxo-3-{[4-(trifluoromethyl)phenyl]amino}-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-3-fluoro-4-{3-[(2-methyl-1,1-dioxido-2,3-dihydro-1,2-benzisothiazol-5-yl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-3-methyl-4-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(4-oxo-3-((1-oxo-2,3-dihydro-1*H*-inden-5-yl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-{[3-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-3-fluoro-4-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-{[4-(dimethylsulfamoyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-3-fluoro-4-[4-oxo-3-(phenylamino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-3-fluoro-4-[4-oxo-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-4,5-dihydro-*1H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate;

tert-butyl 4-{3-[(2-*tert*-butyl-1,1-dioxido-2,3-dihydro-1,2-benzisothiazol-5-yl)amino]-4-oxo-4,5-dihydro-*1H*-pyrazolo[4,3-*c*]pyridin-1-yl}-4-(cyanomethyl)-3-fluoropiperidine-1-carboxylate;

tert-butyl 4-{3-[(2-*tert*-butyl-1,1-dioxido-2,3-dihydro-1,2-benzisothiazol-5-yl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}-4-(cyanomethyl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-{[1,1-dioxido-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1,2-benzisothiazol-5-yl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((1,1-dioxido-2-(2,2,2-trifluoroethyl)-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

2-(4-(3-((2-(*tert*-butyl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1-(2,2-difluoropropanoyl)piperidin-4-yl)acetonitrile;

2-(3-(4-oxo-3-(phenylamino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-3-yl)acetonitrile;

4-((1-(3-(cyanomethyl)tetrahydro-2*H*-pyran-3-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide;

2-(3-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-3-yl)acetonitrile;

methyl 5-(cyanomethyl)-5-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate;

tert-butyl 5-(cyanomethyl)-5-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate;

tert-butyl 5-(3-((2-(*tert*-butyl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-5-(cyanomethyl)tetrahydro-2*H*-pyran-2-carboxylate;

tert-butyl 5-(cyanomethyl)-5-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate;

tert-butyl 5-(cyanomethyl)-5-(3-((1,1-dioxido-2-(2,2,2-trifluoroethyl)-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate;

tert-butyl 3-(cyanomethyl)-3-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)azetidine-1-carboxylate;

tert-butyl 3-(cyanomethyl)-3-{3-[(2-fluoropyridin-4-yl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}azetidine-1-carboxylate;

tert-butyl 3-(cyanomethyl)-3-[4-oxo-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]azetidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-{3-[(4-fluorophenyl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)-3-methylphenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 5-(3-((4-1-amino-2,2,2-trifluoroethyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-5-(cyanomethyl)tetrahydro-2*H*-pyran-2-carboxylate;

tert-butyl 5-(cyanomethyl)-5-(4-oxo-3-(phenylamino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate;

tert-butyl 5-(cyanomethyl)-5-(3-((2-methyl-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate;

N-(*tert*-butyl)-4-((1-(4-(cyanomethyl)-1-(2,2-difluoropropanoyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)benzenesulfonamide;

2-(1-(2,2-difluoropropanoyl)-4-(3-((4-(isopropylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidin-4-yl)acetonitrile;

N-(*tert*-butyl)-4-((1-(4-(cyanomethyl)-1-(2,2-difluoropropanoyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*-methylbenzenesulfonamide;

2-(4-(3-((4-(*tert*-butylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1-(2,2-difluoropropanoyl)piperidin-4-yl)acetonitrile;

tert-butyl 4-(3-(3,5-bis((1*H*-pyrazol-1-yl)methyl)phenylamino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-(3,5-dimethylphenylamino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(3-(3,5-bis((1*H*-1,2,3-triazol-1-yl)methyl)phenylamino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate;

tert-butyl 4-(3-(3,5-bis((2*H*-1,2,3-triazol-2-yl)methyl)phenylamino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate;

tert-butyl 4-(3-(3-((1*H*-1,2,3-triazol-1-yl)methyl)-5-((2*H*-1,2,3-triazol-2-yl)methyl) phenylamino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate;

tert-butyl 4-(3-(*m*-toluidino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-(isoindolin-5-ylamino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl]amino}-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-{[2-(cyclopropylmethyl)-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl]amino}-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-{3-[(2-ethyl-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl)amino]-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate;

methyl 4-(cyanomethyl)-4-[3-[(2-methyl-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl)amino]-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate;

methyl 4-{3-[(2-*tert*-butyl-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl)amino]-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl}-4-(cyanomethyl)piperidine-1-carboxylate;

methyl 4-{3-[(2-ethyl-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl)amino]-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl}-4-(cyanomethyl)piperidine-1-carboxylate;

methyl 4-(cyanomethyl)-4-(3-{[2-(2-methylpropyl)-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl]amino}-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

methyl 4-(cyanomethyl)-4-(3-{[2-(cyclopropylmethyl)-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl]amino}-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

methyl 4-(cyanomethyl)-4-(3-{[2-(cyclopentylmethyl)-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl]amino}-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-[4-oxo-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-{3-[(2-fluoropyridin-4-yl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate;

4-(1-(1-(cyanomethyl)cyclohexyl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-ylamino)-*N*,*N*-dimethylbenzenesulfonamide;

2-(1-(3-((2-(*tert*-butyl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile;

2-(1-(3-((2-methyl-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile;

tert-butyl 4-(cyanomethyl)-4-(3-((1,1-dioxido-2,3-dihydrobenzo[*b*]thiophen-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

2-(8-(4-oxo-3-((4-(trifluoromethyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1,4-dioxaspiro[4.5]decan-8-yl)acetonitrile;

tert-butyl 4-(cyanomethyl)-4-(4-oxo-3-((4-(((2,2,2-trifluoroethyl)amino)methyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((4-(*N*-isopropylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(3-((4-(*N*-benzylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((4-(*N*-(cyclopropylmethyl) sulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((4-(*N*-(2-methoxyethyl)sulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((4-(*N*-cyclohexylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(4-oxo-3-((4-(piperidin-1-ylsulfonyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((4-(morpholinosulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((3-fluoro-4-(*N*-isopropylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((4-(*N*-(cyclopropylmethyl)sulfamoyl)-3-fluorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

(4-{3-[(4-fluorophenyl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidin-4-yl)acetonitrile;

[1-(cyclopropylcarbonyl)-4-{3-[(4-fluorophenyl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidin-4-yl]acetonitrile;

4-({1-[1-benzyl-4-(cyanomethyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(4-methylbenzyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{4-(cyanomethyl)-1-[4-(trifluoromethyl)benzyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{4-(cyanomethyl)-1-[4-(1-methylethyl)benzyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{4-(cyanomethyl)-1-[4-(1-methylethyl)benzyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzene sulfonamide;

4-[(1-{4-(cyanomethyl)-1-[4-(1methylethoxy)benzyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzene sulfonamide;

4-({1-[4-(cyanomethyl)-1-(4-fluorobenzyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(3-fluorobenzyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzene sulfonamide;

4-({1-[4-(cyanomethyl)-1-(2-fluorobenzyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(2,6-difluorobenzyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzene sulfonamide;

4-({1-[4-(cyanomethyl)-1-(2,3,6-trifluorobenzyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(1,3-oxazol-2-ylmethyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(4-isoxazol-3-ylbenzyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{4-(cyanomethyl)-1-[4-(2-oxopyrrolidin-1-yl)benzyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(3-phenylpropyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzene sulfonamide;

4-({1-[4-(cyanomethyl)-1-(1*H*-indol-4-ylmethyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-((1-(4-(cyanomethyl)-1-(1-(2,6-difluorophenyl)ethyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-((1-(4-(cyanomethyl)-1-phenethylpiperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide;

3-({1-[4-(cyanomethyl)-1-(pyridin-3-ylmethyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-propanoylpiperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(3,3,3-trifluoropropanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(methoxyacetyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(*N*,*N*-dimethylglycyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(cyclopropylcarbonyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{4-(cyanomethyl)-1-[(3,3-difluorocyclobutyl)carbonyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(cyclohexylcarbonyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{4-(cyanomethyl)-1-[tricyclo[3.3.1.13,7]dec-1-ylcarbonyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(cyclopropylacetyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(3-cyclopropylpropanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(phenylcarbonyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{1-[(4-chlorophenyl)carbonyl]-4-(cyanomethyl)piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{1-[(3-chlorophenyl)carbonyl]-4-(cyanomethyl)piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{1-[(2-chlorophenyl)carbonyl]-4-(cyanomethyl)piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-{[4-(trifluoromethyl)phenyl]acetyl}piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(3-phenylpropanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(2,3-dihydro-1*H*-inden-2-ylcarbonyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{4-(cyanomethyl)-1-[(2-oxopyrrolidin-1-yl)acetyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(tetrahydro-2*H*-pyran-4-ylcarbonyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(4,4,4-trifluorobutanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(3-cyanopropanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(3,3-dimethylbutanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-((1-(4-(cyanomethyl)-1-(2-(methylthio)propanoyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-((1-(1-(2-cyanoacetyl)-4-(cyanomethyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide;

methyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

phenyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

4-fluorophenyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

neopentyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

ethyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

isopropyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

methyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

2-methylcyclopentyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

2-(methylthio)ethyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tetrahydro-2*H*-thiopyran-4-yl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

1-methoxypropan-2-yl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tetrahydrofuran-3-yl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tetrahydro-2*H*-pyran-4-yl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

1,1,1-trifluoropropan-2-yl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

1-(pyridin-2-yl)ethyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

1-cyanoethyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tetrahydrofuran-3-yl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

2,2,2-trifluoroethyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

4-((1-(4-(cyanomethyl)-1-((2,2,2-trifluoroethyl)sulfonyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-((1-(4-(cyanomethyl)-1-(cyclopropylsulfonyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide;

2-(4-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)acetonitrile;

6-(4-(cyanomethyl)-4-(3-((4(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidin-1-yl)nicotinonitrile;

6-(4-(cyanomethyl)-4-(3-((4((difluoromethyl)sulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidin-1-yl)nicotinonitrile;

2-(4-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1-(5(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)acetonitrile;

2-(1-(2,2-difluoropropanoyl)-4-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidin-4-yl)acetonitrile;

2-(4-(3-fluoroazetidin-1-yl)-1-(4-oxo-3-((4-(trifluoromethyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile;

2-(1-(4-oxo-3-((4-(trifluoromethyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(phenylamino)cyclohexyl)acetonitrile;

2-(4-hydroxy-1-(4-oxo-3-((4-(trifluoromethyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile;

2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(3-fluoroazetidin-1-yl)cyclohexyl)acetonitrile;

2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(3-methoxyazetidin-1-yl)cyclohexyl)acetonitrile;

2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-((2,2,2-trifluoroethyl)amino)cyclohexyl)acetonitrile;

2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-hydroxycyclohexyl)acetonitrile;

2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(phenylamino)cyclohexyl)acetonitrile;

2-(4-(3-methoxyazetidin-1-yl)-1-(4-oxo-3-((4-(trifluoromethoxy)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile;

2-(1-(4-oxo-3-((4-(trifluoromethoxy)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(phenylamino)cyclohexyl)acetonitrile;

2-(4-(cyclohexylamino)-1-(4-oxo-3-((4-(trifluoromethoxy)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile;

2-(1-(3-((4-chloro-3-fluorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyclohexylamino)cyclohexyl)acetonitrile;

2-(1-(3-((4-chloro-3-fluorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(3-methoxyazetidin-1-yl)cyclohexyl)acetonitrile;

2-(1-(3-((4-chloro-3-fluorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(phenylamino)cyclohexyl)acetonitrile;

2-(1-(3-((4-((difluoromethyl)sulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(3-fluoroazetidin-1-yl)cyclohexyl)acetonitrile;

4-((1-(1-(cyanomethyl)-4-(3-fluoroazetidin-1-yl)cyclohexyl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N,N*-dimethylbenzenesulfonamide;

2-(4-(3-fluoroazetidin-1-yl)-1-(3-((2-methyl-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-6-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile;

2-(4-(dimethylamino)-1-(3-((2-methyl-1,1-dioxido-2,3-dihydrobenzo-[*d*]isothiazol-6-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile;

2-(4-(3-fluoroazetidin-1-yl)-1-(3-((2-methyl-1,1-dioxido-2,3-dihy-drobenzo[*d*]isothiazol-6-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile;

2-(1-(3-((2-(*tert*-butyl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(dimethylamino)cyclohexyl)acetonitrile; and

4-((1-(1-(cyanomethyl)-4-oxocyclohexyl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N,N*-dimethylbenzenesulfonamide.

The invention also encompasses pharmaceutical compositions containing a compound of formula I, and methods for treatment or prevention of JAK mediated diseases using compounds of formula I.

The invention is described using the following definitions unless otherwise indicated.

As used herein except where noted, "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups, including all isomers, having the specified number of carbon atoms. Commonly used abbreviations for alkyl groups are used throughout the specification, e.g. methyl may be represented by “Me” or CH_3, ethyl may be represented by “Et” or CH_2CH_3, propyl may be represented by “Pr” or $CH_2CH_2CH_3$, butyl may be represented by “Bu” or $CH_2CH_2CH_2CH_3$, etc. “$C_{1\text{-}6}$ alkyl” (or “C_1-C_6 alkyl”) for example, means linear or branched chain alkyl groups, including all isomers, having the specified number of carbon atoms. $C_{1\text{-}6}$ alkyl includes all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. “$C_{1\text{-}4}$ alkyl” means n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl.

The term “alkylene” refers to both branched- and straight-chain saturated aliphatic hydrocarbon groups, including all isomers, having the specified number of carbons, and having two terminal end chain attachments. For illustration, the term “unsubstituted A-C4alkylene-B” represents A-CH_2-CH_2-CH_2-CH_2-B.

The term "alkoxy" represents a linear or branched alkyl group of indicated number of carbon atoms attached through an oxygen bridge.

"Acyl" means a –C(O)R radical where R is optionally substituted alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl heteroaryl, etc.

"Acylamino" means a –NRR' radical where R is H, OH, or alkoxy and R' is acyl, as defined herein.

The term "alkyl" refers to an aliphatic hydrocarbon group which may be straight or branched and having the indicated number of carbon atoms. Non-limiting examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *s*- and *t*-butyl, pentyl, hexyl, and the like.

The term "heteroalkyl" refers to an alkyl group where 1, 2, or 3 of the carbon atoms is substituted by a heteroatom independently chosen from N, O, or S.

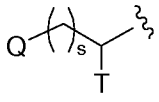
"Alkenyl" refers to an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and having the indicated number of carbon atoms. Preferably alkenyl contains one carbon to carbon double bond, and up to four nonaromatic carbon-carbon double bonds may be present. Examples of alkenyl groups include ethenyl, propenyl, *n*-butenyl, 2-methyl-1-butenyl, 3-methylbut-2-enyl, *n*-pentenyl, octenyl and decenyl.

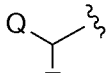
"Alkynyl" refers to an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and having the indicated number of carbon atoms. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl.

"Alkoxy" refers to an alkyl-O- group in which the alkyl group is as described above. C_{1-6}alkoxy, for example, includes methoxy, ethoxy, propoxy, isopropoxy, and the like.

"Alkoxyalkyl" refers to an alkyl group as described above in which one or more (in particular 1 to 3) hydrogen atoms have been replaced by alkoxy groups. Examples include CH_2OCH_3, $CH_2CH_2OCH_3$ and $CH(OCH_3)CH_3$.

"Aminoalkyl" refers to an alkyl group as described above in which one hydrogen atom has been replaced by an amino, monoalkylamino or dialkylamino group. Examples include CH_2NH_2, $CH_2CH_2NHCH_3$ and $CH(N(CH_3)_2)CH_3$.

The term "C_0" as employed in expressions such as "C_{0-6} alkyl" means a direct covalent bond; or when the term appears at the terminus of a substituent, C_{0-6} alkyl means hydrogen or C1-6alkyl. Similarly, when an integer defining the presence of a certain number of atoms in a group is equal to zero, it means that the atoms adjacent thereto are connected directly by a bond. For example, in the structure 

, wherein s is an integer equal to zero, 1 or 2, the structure is 

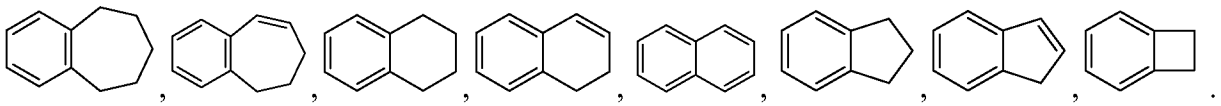
when s is zero.

The term "C_{3-8} cycloalkyl" (or "C_3-C_8 cycloalkyl") means a cyclic ring of an alkane having three to eight total carbon atoms (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl). The terms "C_{3-7} cycloalkyl", "C_{3-6} cycloalkyl", "C_{5-7} cycloalkyl" and the like have analogous meanings.

The term "halogen" (or "halo") refers to fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro (F), chloro (Cl), bromo (Br), and iodo (I)).

The term "aryl" refers to aromatic mono- and poly-carbocyclic ring systems, wherein the individual carbocyclic rings in the polyring systems are fused or attached to each other via a single bond. Suitable aryl groups include phenyl, naphthyl, 2,3-dihydro-1*H*-indenyl, and biphenyl.

The term "carbocycle" (and variations thereof such as "carbocyclic" or "carbocyclyl") as used herein, unless otherwise indicated, refers to (i) a C_3 to C_8 monocyclic, saturated or unsaturated ring or (ii) a C_7 to C_{12} bicyclic saturated or unsaturated ring system. Each ring in (ii) is either independent of, or fused to, the other ring, and each ring is saturated or unsaturated. The carbocycle may be attached to the rest of the molecule at any carbon atom which results in a stable compound. The fused bicyclic carbocycles are a subset of the carbocycles; i.e., the term "fused bicyclic carbocycle" generally refers to a C_7 to C_{10} bicyclic ring system in which each ring is saturated or unsaturated and two adjacent carbon atoms are shared by each of the rings in the ring system. A fused bicyclic carbocycle in which one ring is saturated and the other is saturated is a saturated bicyclic ring system. A fused bicyclic carbocycle in which one ring is benzene and the other is saturated is an unsaturated bicyclic ring system. A fused bicyclic carbocycle in which one ring is benzene and the other is unsaturated is an unsaturated ring system. Saturated carbocyclic rings are also referred to as cycloalkyl rings, e.g., cyclopropyl, cyclobutyl, etc. Unless otherwise noted, carbocycle is unsubstituted or substituted with C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, aryl, halogen, NH_2 or OH. A subset of the fused bicyclic unsaturated carbocycles are those bicyclic carbocycles in which one ring is a benzene ring and the other ring is saturated or unsaturated, with attachment via any carbon atom that results in a stable compound. Representative examples of this subset include the following:



"Cyanoalkyl" refers to an alkyl group as described above in which one hydrogen atom has been replaced by a cyano group. Examples include CH_2CN, CH_2CH_2CN and $CH(CN)CH_3$.

"Cycloalkyl" means a carbocyclic ring system having 3 to 12 ring carbon atoms; said ring system may be (a) a monocyclic saturated carbocycle optionally fused to a benzene or a partially unsaturated carbocycle, or (b) a bicyclic saturated carbocycle. For a bicyclic system, within either (a) or (b), the rings are fused across two adjacent ring carbon atoms (e.g., decalin), at one ring carbon atom (e.g., spiro[2.2]pentane), or are bridged groups (e.g., norbornane). Additional examples within the above meaning include, but are not limited to, cyclopropane, cyclobutane, cyclopentane, cyclohexane, perhydroindan, decalin, spiro[4.5]decane, bicyclo[2.2.2]octane, and the like.

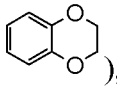
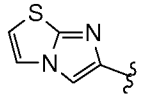
"Haloalkyl" refers to an alkyl group as described above wherein one or more (in particular 1 to 5) hydrogen atoms have been replaced by halogen atoms, with up to complete substitution of all hydrogen atoms with halo groups. C_{1-6}haloalkyl, for example, includes $-CF_3$, $-CF_2CF_3$, $CHFCH_3$, and the like.

"Heterocycle", "heterocyclic" or "heterocyclyl" represents a monocyclic or bicyclic 3-12 membered ring system in which at least one ring is non-aromatic (saturated or partially unsaturated) and containing at least one heteroatom selected from O, S and N. In a bicyclic ring system, the second ring may be a heteroaryl, heterocycle or a saturated, partially unsaturated or aromatic carbocycle, and the point(s) of attachment to the rest of the molecule may be on either ring. "Heterocyclyl" therefore includes heteroaryls, as well as dihydro and tetrathydro analogs thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

Examples of heterocycles (heterocyclyl) include, but are not limited to, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, dihydroimidazolyl, dihydroindolyl, 1,2,3,4-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, 2,3-dihydrobenzofuranyl, benzo-1,4-dioxanyl, benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridinyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, aziridinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and *N*-oxides thereof.

Saturated heterocyclics form a subset of the heterocycles; i.e., the terms "saturated heterocyclic and (C_{3-12})heterocycloalkyl" generally refers to a heterocycle as defined above in which the entire ring system (whether mono- or poly-cyclic) is saturated. The term "saturated heterocyclic ring" refers to a 4- to 8-membered saturated monocyclic ring or a stable 7- to 12-membered bicyclic ring system which consists of carbon atoms and one or more heteroatoms selected from N, O and S. Representative examples include piperidinyl, piperazinyl, azepanyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl (or tetrahydrofuranyl)

Heteroaromatics form another subset of the heterocycles; i.e., the term "heteroaromatic" (alternatively "heteroaryl") generally refers to a heterocycle as defined above in which the entire ring system (whether mono- or poly-cyclic) is an aromatic ring system. The term "heteroaromatic ring" refers a 5- or 6-membered monocyclic aromatic ring or a 7- to 12-membered bicyclic which consists of carbon atoms and one or more heteroatoms selected from N, O and S. For a bicyclic heteroaryl only one of the rings need to be heteroaromatic, the second ring may be a heteroaromatic or an aromatic, saturated, or partially unsatuated carbocycle, and the point(s) of attachment to the rest of the molecule may be on either ring. In the case of substituted heteroaryl rings containing at least one nitrogen atom (e.g., pyridine), such substitutions can be those resulting in *N*-oxide formation. Examples of heteroaryl include, but are not limited to, furanyl, thienyl (or thiophenyl), pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolinyl, isoquinolinyl, naphthyridinyl, benzothienyl, benzofuranyl, benzimidazole, benzpyrazolyl, indolyl, isoindolyl, indolizinyl, indazolyl, purinyl, quinolizinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzoxazolyl, benzisoxazolyl, 5,6,7,8-tetrahydroquinolinyl, imidazo[1,2-*a*]pyridinyl, imidazo[1,2-*a*]-pyrimidinyl, 5,6-dihydropyrrolo[1,2-*b*]pyrazolyl, pyrrolo[3,2-*c*]pyridinyl, pyrrolo[2,3-*b*]pyridinyl, thieno[2,3-*b*]pyrrolyl, furopyridine and thienopyridine.

Representative examples of bicyclic heterocycles include benzotriazolyl, indolyl, isoindolyl, indazolyl, indolinyl, isoindolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, chromanyl, isochromanyl, tetrahydroquinolinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo-1,4-dioxinyl (i.e., ), imidazo(2,1-*b*)(1,3)thiazole, (i.e., ), and benzo-1,3-dioxolyl (i.e., ). In certain contexts herein,  is alternatively referred to as phenyl having as a substituent methylenedioxy attached to two adjacent carbon atoms.

Non-limiting examples of substituted heteroaryls include: isoindolinone, isoindolin-1-one, 2,3-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-4(5*H*)-one, 2,3,4,5-tetrahydrobenzo[*d*]isothiazole 1,1-dioxide, and 2,3,4,5-tetrahydrobenzo[*b*]thiophene 1,1-dioxide.

"Hydroxyalkyl" refers to an alkyl group as described above in which one or more (in particular 1 to 3) hydrogen atoms have been replaced by hydroxy groups. Examples include CH_2OH, CH_2CHOH and $CHOHCH_3$.

"Alkylene," "alkenylene," "alkynylene," "cycloalkylene," "arylene," "heteroarylene," and "heterocyclylene" refer to a divalent radical obtained by the removal of one hydrogen atom from an alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl group, respectively, each of which is as defined above.

Unless expressly stated to the contrary, an "unsaturated" ring is a partially or fully unsaturated ring. For example, an "unsaturated monocyclic C_6 carbocycle" refers to cyclohexene, cyclohexadiene, and benzene.

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heterocycle described as containing from "1 to 4 heteroatoms" means the heterocycle can contain 1, 2, 3 or 4 heteroatoms.

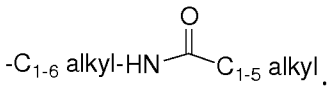
When any variable occurs more than one time in any constituent or in any formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The term "sulfamoyl" is a suffix to denote radicals derived from sulfamide such as $-SO_2NH_2$, $-SO_2NHR$ and $-SO_2N(RR^1)$.

The term "substituted" (e.g., as in "aryl which is optionally substituted with one or more substituents ...") includes mono- and poly-substitution by a named substituent to the extent such single and multiple substitution (including multiple substitution at the same site) is chemically allowed.

The term "oxy" means an oxygen (O) atom. The term "thio" means a sulfur (S) atom. The term "oxo" means "=O". The term "carbonyl" means "C=O."

When any variable (e.g., R^2, R^3, etc.) occurs more than one time in any substituent or in formula I its definition in each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. For example, a C_{1-5} alkylcarbonylamino C_{1-6} alkyl substituent is equivalent to 

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In choosing compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. R^1, R^2, R^3, etc., are to be chosen in conformity with well-known principles of chemical structure connectivity.

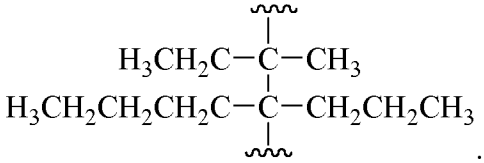
Lines drawn into the ring systems from substituents indicate that the indicated bond can be attached to any of the substitutable ring atoms. If the ring system is polycyclic, it is intended that the bond be attached to any of the suitable carbon atoms on the proximal ring only.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups can be on

the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted with one or more substituents" should be taken to be equivalent to the phrase "optionally substituted with at least one substituent" and in such cases one embodiment will have from zero to three substituents.

Structural representations of compounds having substituents terminating with a methyl group may display the terminal methyl group either using the characters "CH_3", e.g. "-CH_3" or using a straight line representing the presence of the methyl group, e.g. "——", i.e., "§——CH_3" and "§——" have equivalent meanings.

For variable definitions containing terms having repeated terms, e.g., $(CR^iR^j)_r$, where r is the integer 2, R^i is a defined variable, and R^j is a defined variable, the value of R^i may differ in each instance in which it occurs, and the value of R^j may differ in each instance in which it occurs. For example, if R^i and R^j are independently selected from the group consisting of methyl, ethyl, propyl and butyl, then $(CR^iR^j)_2$ can be



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"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"Therapeutically effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term "treatment" or "treating" includes alleviating, ameliorating, relieving or otherwise reducing the signs and symptoms associated with a disease or disorder.

The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of formula I, and pharmaceutically acceptable excipients.

The term "optionally substituted" means "unsubstituted or substituted," and therefore, the generic structural formulas described herein encompasses compounds containing the specified optional substituent as well as compounds that do not contain the optional substituent.

Each variable is independently defined each time it occurs within the generic structural formula definitions. For example, when there is more than one substituent for aryl/heteroaryl, each substituent is independently selected at each occurrence, and each substituent can be the same or different from the other(s). As another example, for the group -(CR^3R^3)$_2$-, each occurrence of the two R^3 groups may be the same or different. As used herein, unless explicitly stated to the contrary, each reference to a specific compound of the present invention or a generic formula of compounds of the present invention is intended to include the compound(s) as well as pharmaceutically acceptable salts thereof.

In one embodiment of the invention, A is selected from phenyl, methyl, ethyl, pyridinyl, cyclobutyl, cyclopropyl, cyclopropylmethyl, dihydroisoindolyl, dihydrobenzisothiazolyl, dihydroindenyl, isoindolyl, dihydro[*b*]thiophenyl, 2,3-dihydrobenzo[*d*]isothiazole-1,1-dioxide 1-oxo-2,3-dihydro-1*H*-indene and 1,1-dioxido-2,3-dihydrobenzo[*b*]thiophene.

In an embodiment of the invention, R^2 and R^3 are each independently selected from hydrogen, methyl, ethyl, propyl and hydroxyl. In a variant of this embodiment, R^2 and R^3 are each hydrogen.

In another embodiement, R^2 and R^3 join together with the carbon they are attached to to form a 3 to 6 membered ring.

In one embodiment of the invention, X_1, X_2, X_3, and X_4 are joined together to from a ring system optionally substituted with 0, 1, 2, 3, or 4 R^4, and wherein two R^4 together with the ring atoms to which they are attached may optionally form a second ring, selected from: piperidinyl, azetidinyl, tetrahydropyranyl, tetrahydro-2*H*-pyranyl, and 1,4-dioxaspiro[4.5]decanyl.

In another embodiement, X_1, X_2, X_3, and X_4 are joined together to from a ring system optionally substituted with 0, 1, 2, 3, or 4 R^4 selected from tetrahydropyranyl, tetrahydro-2*H*-pyranyl, and piperidinyl. In a variant of this embodiment, the ring system is selected from tetrahydropyranyl, tetrahydro-2*H*-pyranyl, and piperidinyl.

In one embodiment of the invention, n is 0, 1, 2, 3, or 4. In one embodiment of the invention, n is 0, 1, 2, or 3. In a variant of this embodiment, n is 0, 1, or 2.

In one embodiment of the invention, m is 0, 1, 2, 3 or 4. In one embodiment of the invention, m is 0, 1, 2, or 3. In a variant of this embodiment, m is 0, 1, or 2.

In one embodiment of the invention, p is 1, 2, 3 or 4.

In one embodiment of the invention, p is 0, 1, 2, or 3. In a variant of this embodiment, p is 1, 2, or 3.

In one embodiment of the invention, R^4 is selected from: halogen, oxo (=O), $C_{1\text{-}10}$ alkyl(oxy)$_{0\text{-}1}$(carbonyl)$_{0\text{-}1}C_{0\text{-}10}$ alkyl, $C_{1\text{-}10}$ heteroalkyl(oxy)$_{0\text{-}1}$(carbonyl)$_{0\text{-}1}C_{0\text{-}10}$ alkyl, aryl $C_{0\text{-}10}$ alkyl(oxy)$_{0\text{-}1}$(carbonyl)$_{0\text{-}1}C_{0\text{-}10}$ alkyl, $C_{3\text{-}8}$cycloalkyl $C_{0\text{-}10}$

alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$C$_{0-10}$ alkyl, heteroaryl C$_{0-10}$ alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$C$_{0-10}$ alkyl, (C$_{3-8}$)heterocycloalkyl C$_{0-10}$ alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$C$_{0-10}$ alkyl, C$_{3-8}$ cycloalkyl C$_{0-10}$ alkylaminoC$_{0-10}$ alkyl, aryl C$_{0-10}$ alkylaminoC$_{0-10}$ alkyl, heteroaryl C$_{0-10}$ alkylaminoC$_{0-10}$ alkyl, (C$_{3-8}$)heterocycloalkyl C$_{0-10}$ alkylaminoC$_{0-10}$ alkyl, C$_{1-10}$ alkylsulfonyl, C$_{1-10}$ heteroalkylsulfonyl, (C$_{3-8}$)cycloalkylC$_{0-10}$alkylsulfonyl, (C$_{3-8}$)cycloheteroalkylC$_{0-10}$alkylsulfonyl, heteroarylC$_{0-10}$ alkylsulfonyl, arylC$_{0-10}$ alkylsulfonyl, -SO$_2$NH$_2$, -SO$_2$NH(C$_{1-6}$alkyl), -SO$_2$N(C$_{1-6}$alkyl)$_2$, C$_{0-10}$ alkylsulfamoyl, C$_{1-10}$ heteroalkylsulfamoyl, (C$_{3-8}$)cycloalkylC$_{0-10}$ alkylsulfamoyl, (C$_{3-8}$)cycloheteroalkylC$_{0-10}$ alkylsulfamoyl, heteroarylC$_{0-10}$ alkylsulfamoyl, arylC$_{0-10}$ alkylsulfamoyl, (C$_{0-10}$ alkyl)$_{1-2}$ amino, -CO$_2$(C$_{0-10}$ alkyl), -(C$_{0-10}$ alkyl)CO$_2$H, hydroxy, -(C$_{1-10}$ alkyl)OH, C$_{0-10}$ alkylalkoxy, and C$_{1-6}$haloalkyl; wherein R^4 is optionally substituted with 1, 2, 3, or 4 R^6 substituents and two R^4 together with the ring atoms to which they are attached may optionally join together to form a ring.

In one embodiment of the invention, R^4 is selected from: halogen, C$_{1-10}$alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$C$_{0-10}$ alkyl, C$_{1-10}$ heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$C$_{0-10}$ alkyl, aryl C$_{0-10}$ alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$C$_{0-10}$ alkyl, C$_{3-8}$ cycloalkyl C$_{0-10}$ alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$C$_{0-10}$ alkyl, heteroaryl C$_{0-10}$ alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$C$_{0-10}$ alkyl, (C$_{3-8}$)heterocycloalkyl C$_{0-10}$ alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$C$_{0-10}$ alkyl, C$_{3-8}$ cycloalkyl C$_{0-10}$ alkylaminoC$_{0-10}$ alkyl, aryl C$_{0-10}$ alkylaminoC$_{0-10}$ alkyl, C$_{1-10}$ alkylsulfonyl, C$_{1-10}$ heteroalkylsulfonyl, (C$_{3-8}$)cycloalkylC$_{0-10}$alkylsulfonyl, and (C$_{3-8}$)cycloheteroalkylC$_{0-10}$alkylsulfonyl, wherein R^4 is optionally substituted with 1, 2, 3, or 4 R^6 substituents, and two R^4 together with the ring atoms to which they are attached may optionally join together to form a ring.

In one embodiment of the invention, R^4 is selected from: *tert*-butoxycarbonyl, fluoro, difluoropropanoyl, methoxycarbonyl, *tert*-butoxycarbony, difluoropropanoyl, methoxy, ethoxy, cyclopropylcarbonyl, benzyl, oxazolylmethyl, phenylpropyl, indolylmethyl, phenylethyl, pyridinylmethyl, propanoyl, ethylcarbonyl, trifluropropanoyl, methoxyacetyl, dimethylglycyl, dimethylpropanoyl, cyclobutylcarbonyl, cyclohexylcarbonyl, cyclopropylacetyl, cyclopropylpropanoyl, phenylcarbonyl, phenylacetyl, 2,3-dihydro-indenyl, pyrrolidinylacetyl, tetrahydropyranylcarbonyl, butanoyl, propanoyl, dimethylbutanoyl, 3,3-dimethylbutanoyl, propanoyl, methylthio, acetyl, phenoxycarbonyl, 2,2,2-trimethylethoxycarbonyl, trimethylethoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, ethoxycarbonyl,

cyclopentyloxycarbonyl, ethoxycarbonyl, methylethoxycarbonyl, tetrahydrofuranyloxycarbonyl, tetrahydropyranyloxycarbonyl, pyridinylethoxycarbonyl, (trifluoroethyl)sulfonyl, (2,2,2-trifluoroethyl)sulfonyl, cyclopropylsulfonyl, pyridinyl, *tert*-butylcarbonyl, azetindinyl, phenylamino, ethylamino, methylamino, and cyclohexylamino; wherein R^4 is optionally substituted with 0, 1, 2, 3, or 4 R^6 substituents, and two R^4 together with the ring atoms to which they are attached may optionally join together to form a ring.

In one embodiment, R^5 is selected from: halogen, oxo (=O), C_{1-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{1-10} heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{2-10} alkenyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, aryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{3-8} cycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, (C_{3-8})heterocycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl, (C_{1-10})heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl, -SF_5, C_{1-10} alkylsulfonyl, C_{1-10} heteroalkylsulfonyl, (C_{3-8})cycloalkylC_{0-10}alkylsulfonyl, (C_{3-8})cycloheteroalkylC_{0-10}alkylsulfonyl, heteroarylC_{0-10} alkylsulfonyl, arylC_{0-10} alkylsulfonyl, C_{0-10} alkylsulfamoyl, C_{1-10} heteroalkylsulfamoyl, (C_{3-8})cycloalkylC_{0-10} alkylsulfamoyl, (C_{3-8})cycloheteroalkylC_{0-10} alkylsulfamoyl, heteroarylC_{0-10} alkylsulfamoyl, arylC_{0-10} alkylsulfamoyl, (C_{0-10} alkyl)$_{1-2}$ amino, -CO_2(C_{0-10} alkyl), -(C_{0-10} alkyl)CO_2,-SO_2NH_2, -SO_2NH(C_{1-6}alkyl), -SO_2N(C_{1-6}alkyl)$_2$, H, -SO_2CF_3, -SO_2CF_2H, hydroxy, -(C_{1-10} alkyl)OH, C_{0-10} alkylalkoxy, cyano, (C_{1-6}alkyl)cyano, and C_{1-6}haloalkyl; and wherein R^5 is optionally substituted with 0, 1, 2, 3, or 4 R^6 substituents.

In another embodiment, R^5 is selected from: halogen, oxo (=O), C_{1-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{3-8} cycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl, -SF_5, C_{1-10} alkylsulfonyl, (C_{3-8})cycloalkylC_{0-10}alkylsulfonyl, (C_{3-8})cycloheteroalkylC_{0-10}alkylsulfonyl, C_{0-10} alkylsulfamoyl, (C_{3-8})cycloalkylC_{0-10} alkylsulfamoyl, arylC_{0-10} alkylsulfamoyl,-(C_{1-10} alkyl)OH, and C_{1-6}haloalkyl; and

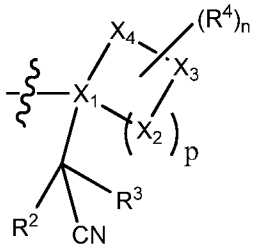
wherein R^5 is optionally substituted with 0, 1, 2, 3, or 4 R^6 substituents.

In one embodiment, wherein R^5 is selected from: oxo, trifluoromethyl, methoxycarbonyl, fluoro, dimethylsulfamoyl, hydroxyethyl, sulfamoyl, trifluoroethyl, methylsulfonyl, methyl,

pentafluorosulfanyl, 2,2,2-trifluoroethyl, *tert*-butyl, (trifluoromethyl)sulfonyl, methylamino, *tert*-butylsulfamoyl, isopropylsulfonyl, *tert*-butylsulfamoyl, pyrazolylmethyl, triazolylmethyl, 1,2,3-triazolylmethyl, isobutyl, cyclopropylmethyl, ethyl, cyclopentylmethyl, isopropylsulfamoyl, benzylsulfamoyl, (cyclopropylmethyl)sulfamoyl, (methoxyethyl)sulfamoyl, cyclohexylsulfamoyl, piperidinylsulfonyl, morpholinosulfonyl, difluoromethylsulfonyl, chloro, and methoxy; wherein R^5 is optionally substituted with 0, 1, 2, 3, or 4 R^6 substituents.

In one embodiment, R^6 is independently selected from: halogen, C_{1-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{1-10} heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, aryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{3-8} cycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, (C_{3-8})heterocycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{1-10} alkyl(carbonyl)$_{0-1}$oxyC_{0-10} alkyl, ((C_{0-10})alkyl)$_{1-2}$aminocarbonyloxy, -CO_2(C_{0-10} alkyl), -(C_{0-10} alkyl)CO_2H, oxo (=O), -SO_2NH_2, -$SO_2NH(C_{1-6}$alkyl), -$SO_2N(C_{1-6}$alkyl)$_2$,-SO_2CF_3, -SO_2CF_2H, amino, (C_{0-10} alkyl)$_{1-2}$ amino, hydroxy, (C_{1-10} alkyl)OH, C_{1-10} alkoxy, cyano, and C_{1-6}haloalkyl.

In another embodiment, R^6 is independently selected from: halogen, C_{1-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, oxo (=O), amino, (C_{0-10} alkyl)$_{1-2}$ amino, hydroxy, C_{1-10} alkoxy, cyano, and C_{1-6}haloalkyl.

In one embodiment, the section of formula I, 

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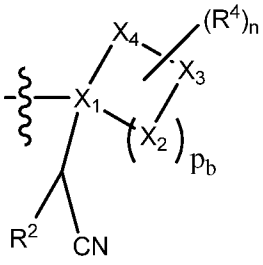
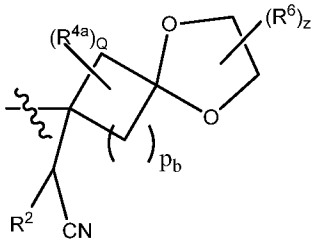
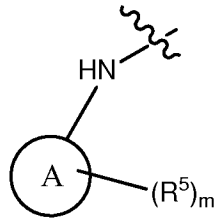


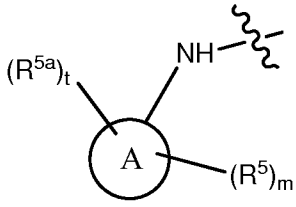
and 

; and

R^2 is hydrogen; Q is 0, 1, 2 or 3; R^{4a} is OH, $C_{(1-4)}$ alkyl, oxo, or halogen; p_b is independently 0, 1, 2, 3, or 4; and Z is 0, 1, or 2, provided that the sum of Q and Z is less than or equal to 4.

In another embodiment of the invention, the portion of formula I, 

, is selected from:



; and t is 0, 1, 2 or 3; m is 0, 1, or 2; and R^{5a} is selected from halogen, methyl, ethyl, oxo, C_{1-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{1-10} heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, aryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{3-8} cycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, and (C_{3-8})heterocycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl; provided that the sum of t plus m is less than or equal to 4.

In a variant of this embodiment, R^{5a} is selected from halogen, methyl, ethyl, oxo, and heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl.

Optical Isomers - Diastereomers - Geometric Isomers – Tautomers

Compounds of formula I contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of formula I, either as single species or mixtures thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist with different points of attachment of hydrogen, referred to as tautomers. Such an example may be a ketone and its enol form known as keto-enol tautomers. The individual tautomers as well as mixture thereof are encompassed with compounds of formula I.

Specific embodiments of the present invention include a compound which is selected from the group consisting of the subject compounds of the examples herein or a pharmaceutically acceptable salt thereof.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as "stereoisomers" including racemates and racemic mixtures, enantiomeric mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the scope of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds. When bonds to the chiral carbon are depicted as straight lines in the formulas of the invention, it is understood that both the (R) and (S) configurations of the chiral carbon, and hence both enantiomers and mixtures thereof, are embraced within the formula. For example, formula I shows the structure of the class of compounds without specific stereochemistry. When the compounds of the present invention contain one chiral center, the term "stereoisomer" includes both enantiomers and mixtures of enantiomers, such as the specific 50:50 mixture referred to as racemic mixtures.

The compounds of formula (I) may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of formula (I) as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of formula (I) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of formula (I) may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

It is also possible that the compounds of formula (I) may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). For example, if a compound of formula (I) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 recommendations. The use of the terms "salt", "solvate", “ester”, "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

In the present application when a particular stereomeric compound is named using an "and" in the stereomeric designation, for example, *tert*-butyl (3*R*,4*S* and 3*S*,4*R*)-4-(cyanomethyl)-3-methyl-4-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate, the "and" indicates a racemic mixture of the enantiomers. That is, the individual enantiomers were not individually isolated.

When the stereomeric nomenclature includes "or", for example, *tert*-butyl 4-(cyanomethyl)-4-[4-oxo-3-({4-[(1*R* or 1*S*)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate, the "or" indicates that chiral resolution of racemate into individual enantiomers was accomplished but the actual optical activity of the specific enantiomer was not nessissarily determined.

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration. If

desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diasteromeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art. Alternatively, any enantiomer of a compound can be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

Salt

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, *N,N'*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethyl-morpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, *p*-toluenesulfonic acid, 1-hydroxy-2-naphthoic acid (xinafoate) and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that, unless otherwise specified, references to the compound of formula I subsets thereof, embodiments thereof, as well as specific compounds are meant to also include the pharmaceutically acceptable salts and stereoisomers thereof.

Furthermore, some of the crystalline forms for compounds of the present invention may exist as polymorphs and as such all forms are intended to be included in the present invention. In addition, some of the compounds of the instant invention may form solvates with water (hydrates) or common organic solvents. Such solvates are encompassed within the scope of this invention.

Labelled Compounds

In the compounds of generic formula I, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic formula I. For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic formula I can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the schemes and examples herein using appropriate isotopically-enriched reagents and/or intermediates.

Utilities

Compound of formula I or its pharmaceutically acceptable salts and pharmaceutical compositions can be used to treat or prevent a variety of conditions or diseases mediated by Janus kinases, in particular diseases or conditions that can be ameliorated by the inhibition of a Janus kinase such as JAK1, JAK2, JAK3 or TYK2. Such conditions and diseases include, but are not limited to:

(1) arthritis, including rheumatoid arthritis, juvenile arthritis, and psoriatic arthritis; (2) asthma and other obstructive airways diseases, including chronic asthma, late asthma, airway hyper-responsiveness, bronchitis, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, recurrent airway obstruction, and chronic obstruction pulmonary disease including emphysema; (3) autoimmune diseases or disorders, including those designated as single organ or single cell-type autoimmune disorders, for example Hashimoto's thyroiditis, autoimmune hemolytic anemia, autoimmune atrophic gastritis of pernicious anemia, autoimmune encephalomyelitis, autoimmune orchitis, Goodpasture's disease, autoimmune thrombocytopenia, sympathetic ophthalmia, myasthenia gravis, Graves' disease, primary biliary cirrhosis, chronic aggressive hepatitis, ulcerative colitis and membranous glomerulopathy, those designated as

involving systemic autoimmune disorder, for example systemic lupus erythematosis, rheumatoid arthritis, Sjogren's syndrome, Reiter's syndrome, polymyositis-dermatomyositis, systemic sclerosis, polyarteritis nodosa, multiple sclerosis and bullous pemphigoid, and additional autoimmune diseases, which can be B-cell (humoral) based or T-cell based, including Cogan's syndrome, ankylosing spondylitis, Wegener's granulomatosis, autoimmune alopecia, Type I or juvenile onset diabetes, and thyroiditis; (4) cancers or tumors, including alimentary/gastro-intestinal tract cancer, colon cancer, liver cancer, skin cancer including mast cell tumor and squamous cell carcinoma, breast and mammary cancer, ovarian cancer, prostate cancer, lymphoma, leukemia, including acute myelogenous leukemia and chronic myelogenous leukemia, kidney cancer, lung cancer, muscle cancer, bone cancer, bladder cancer, brain cancer, melanoma including oral and metastatic melanoma, Kaposi's sarcoma, myelomas including multiple myeloma, myeloproliferative disorders, proliferative diabetic retinopathy, and angiogenic-associated disorders including solid tumors; (5) diabetes, including Type I diabetes and complications from diabetes; (6) eye diseases, disorders or conditions including autoimmune diseases of the eye, keratoconjunctivitis, vernal conjunctivitis, uveitis including uveitis associated with Behcet's disease and lens-induced uveitis, keratitis, herpetic keratitis, conical keratitis, corneal epithelial dystrophy, keratoleukoma, ocular premphigus, Mooren's ulcer, scleritis, Grave's ophthalmopathy, Vogt-Koyanagi-Harada syndrome, keratoconjunctivitis sicca (dry eye), phlyctenule, iridocyclitis, sarcoidosis, endocrine ophthalmopathy, sympathetic ophthalmitis, allergic conjunctivitis, and ocular neovascularization; (7) intestinal inflammations, allergies or conditions including Crohn's disease and/or ulcerative colitis, inflammatory bowel disease, coeliac diseases, proctitis, eosinophilic gastroenteritis, and mastocytosis; (8) neurodegenerative diseases including motor neuron disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia, or neurodegenerative disease caused by traumatic injury, strike, glutamate neurotoxicity or hypoxia; ischemic/reperfusion injury in stroke, myocardial ischemica, renal ischemia, heart attacks, cardiac hypertrophy, atherosclerosis and arteriosclerosis, organ hypoxia, and platelet aggregation; (9) skin diseases, conditions or disorders including atopic dermatitis, eczema, psoriasis, scleroderma, pruritus and other pruritic conditions; (10) allergic reactions including anaphylaxis, allergic rhinitis, allergic dermatitis, allergic urticaria, angioedema, allergic asthma, or allergic reaction to insect bites, food, drugs, or pollen; (11) transplant rejection, including pancreas islet transplant rejection, bone marrow transplant rejection, graft- versus-host disease, organ and cell transplant rejection such as bone marrow, cartilage, cornea, heart, intervertebral disc, islet, kidney, limb, liver, lung, muscle, myoblast, nerve, pancreas, skin, small intestine, or trachea, and xeno transplantation.

Accordingly, another aspect of the present invention provides a method for the treatment or prevention of a JAK-mediated disease or disorder comprising administering to a

mammal in need thereof a therapeutically effective amount of a compound of formula I. In one embodiment such diseases include asthma and rheumatoid arthritis.

Another aspect of the present invention provides for the use of a compound of formula I in the manufacture of a medicament for the treatment or prevention of a JAK-mediated disease or disorder.

One aspect of the invention is the use of a compound of formula I or a pharmaceutically acceptable salt or a stereoisomer thereof in the manufacture of a medicament for the treatment of a disease or a disorder ameliorated byinhibition of Janus kinases JAK1 and JAK2.

Another aspect of the invention is the use of a compound of Formula I or a pharmaceutically acceptable salt or a stereoisomer thereof and a second active agent in the manufacture of a medicament for the treatment of a disease or a disorder ameliorated by inhibition of Janus kinases JAK1 and JAK2.

Dose Ranges

The magnitude of prophylactic or therapeutic dose of a compound of formula I will, of course, vary with the nature and the severity of the condition to be treated and with the particular compound of formula I and its route of administration. It will also vary according to a variety of factors including the age, weight, general health, sex, diet, time of administration, rate of excretion, drug combination and response of the individual patient. In general, the daily dose from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 10 mg per kg. On the other hand, it may be necessary to use dosages outside these limits in some cases.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.05 mg to 5 g, of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 99.95 percent of the total composition. In some cases, the dosage unit forms may contain from about 0.05 to about 3g of active ingredient. Dosage unit forms will generally contain between from about 0.1 mg to about 0.4 g of an active ingredient, typically 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 1 mg, 2 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg, 200 mg, or 400 mg.

Pharmaceutical Compositions

Another aspect of the present invention provides pharmaceutical compositions comprising a compound of formula I with a pharmaceutically acceptable carrier. For the treatment of any of the prostanoid mediated diseases compounds of formula I may be

administered orally, by inhalation spray, topically, parenterally or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water-miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty

acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For

this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Dosage forms for inhaled administration may conveniently be formulated as aerosols or dry powders. For compositions suitable and/or adapted for inhaled administration, it is preferred that the active substance is in a particle-size-reduced form, and more preferably the size-reduced form is obtained or obtainable by micronization.

In one embodiment the medicinal preparation is adapted for use with a pressurized metered dose inhaler (pMDI) which releases a metered dose of medicine upon each actuation. The formulation for pMDIs can be in the form of solutions or suspensions in halogenated hydrocarbon propellants. The type of propellant being used in pMDIs is being shifted to hydrofluoroalkanes (HFAs), also known as hydrofluorocarbons (HFCs). In particular, 1,1,1,2-tetrafluoroethane (HFA 134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA 227) are used in several currently marketed pharmaceutical inhalation products. The composition may include other pharmaceutically acceptable excipients for inhalation use such as ethanol, oleic acid, polyvinylpyrrolidone and the like.

Pressurized MDIs typically have two components. Firstly, there is a canister component in which the drug particles are stored under pressure in a suspension or solution form. Secondly, there is a receptacle component used to hold and actuate the canister. Typically, a canister will contain multiple doses of the formulation, although it is possible to have single dose canisters as well. The canister component typically includes a valve outlet from which the contents of the canister can be discharged. Aerosol medication is dispensed from the pMDI by applying a force on the canister component to push it into the receptacle component thereby opening the valve outlet and causing the medication particles to be conveyed from the valve outlet through the receptacle component and discharged from an outlet of the receptacle. Upon discharge from the canister, the medication particles are "atomized", forming an aerosol. It is intended that the patient coordinate the discharge of aerosolized medication with his or her inhalation, so that the medication particles are entrained in the patient's aspiratory flow and conveyed to the lungs. Typically, pMDIs use propellants to pressurize the contents of the canister and to propel the medication particles out of the outlet of the receptacle component. In pMDIs, the formulation is provided in a liquid or suspension form, and resides within the container along with the propellant. The propellant can take a variety of forms. For example, the propellant can comprise a compressed gas or liquefied gas.

In another embodiment the medicinal preparation is adapted for use with a dry powder inhaler (DPI). The inhalation composition suitable for use in DPIs typically comprises particles of the active ingredient and particles of a pharmaceutically acceptable carrier. The particle size of the active material may vary from about 0.1 μm to about 10 μm; however, for effective delivery to the distal lung, at least 95 percent of the active agent particles are 5 μm or

smaller. Each of the active agent can be present in a concentration of 0.01 - 99%. Typically however, each of the active agents is present in a concentration of about 0.05 to 50%, more typically about 0.2 - 20% of the total weight of the composition.

As noted above, in addition to the active ingredients, the inhalable powder preferably includes pharmaceutically acceptable carrier, which may be composed of any pharmacologically inert material or combination of materials which is acceptable for inhalation. Advantageously, the carrier particles are composed of one or more crystalline sugars; the carrier particles may be composed of one or more sugar alcohols or polyols. Preferably, the carrier particles are particles of dextrose or lactose, especially lactose. In embodiments of the present invention which utilize conventional dry powder inhalers, such as the Handihaler, Rotohaler, Diskhaler, Twisthaler and Turbohaler, the particle size of the carrier particles may range from about 10 microns to about 1000 microns. In certain of these embodiments, the particle size of the carrier particles may range from about 20 microns to about 120 microns. In certain other embodiments, the size of at least 90% by weight of the carrier particles is less than 1000 microns and preferably lies between 60 microns and 1000 microns. The relatively large size of these carrier particles gives good flow and entrainment characteristics. Where present, the amount of carrier particles will generally be up to 95%, for example, up to 90%, advantageously up to 80% and preferably up to 50% by weight based on the total weight of the powder. The amount of any fine excipient material, if present, may be up to 50% and advantageously up to 30%, especially up to 20%, by weight, based on the total weight of the powder. The powder may optionally contain a performance modifier such as L-leucine or another amino acid, and/or metals salts of stearic acid such as magnesium or calcium stearate.

Compounds of formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ambient temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound of formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.) Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

Combinations with Other Drugs

For the treatment and prevention of JAK mediated diseases, compound of formula I may be co-administered with other therapeutic agents. Thus in another aspect the present invention provides pharmaceutical compositions for treating JAK mediated diseases comprising a therapeutically effective amount of a compound of formula I and one or more other therapeutic agents. In particular, for the treatment of the inflammatory diseases rheumatoid arthritis, psoriasis, inflammatory bowel disease, COPD, asthma and allergic rhinitis a compound of formula I may be combined with agents such as: (1) TNF-α inhibitors such as Remicade® and Enbrel®); (2) non-selective COX-I/COX-2 inhibitors (such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin); (3) COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib and etoricoxib); (4) other agents for treatment of rheumatoid arthritis including low dose methotrexate, lefunomide, ciclesonide, hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold; (5) leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as zileuton; (6) LTD4 receptor antagonist such as zafirlukast, montelukast and pranlukast; (7) PDE4 inhibitor such as roflumilast; (8) antihistaminic H1 receptor antagonists such as cetirizine, loratadine, desloratadine, fexofenadine, astemizole, azelastine, and chlorpheniramine; (9) α1- and α2-adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, and ethylnorepinephrine hydrochloride; (10) anticholinergic agents such as ipratropium bromide, tiotropium bromide, oxitropium bromide, aclindinium bromide, glycopyrrolate, pirenzepine, and telenzepine; (11) β-adrenoceptor agonists such as metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, and pirbuterol, or methylxanthanines including theophylline and aminophylline, sodium cromoglycate; (12) insulin-like growth factor type I (IGF-l) mimetic; (13) inhaled glucocorticoid with reduced systemic side effects, such as prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide and mometasone furoate.

SCHEMES AND EXAMPLES

The abbreviations used herein have the following tabulated meanings. Abbreviations not tabulated below have their meanings as commonly used unless specifically stated otherwise.

ACN, MeCN	acetonitrile
BAST	bis(2-methoxyethyl)aminosulfur trifluoride
BOC (N-BOC, n-BOC)	*N-tert*-butoxycarbonyl
t-Bu XPhos	2-di *tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl
Chiral SFC	chiral super critical fluid chromatography
CO_2	carbon dioxide
Cs_2CO_3	cesium carbonate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DIPEA	*N,N*-diisopropylethylamine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DSC	*N,N*-disuccinimidyl carbonate
EDC	3-(ethyliminomethyleneamino)-*N,N*-dimethyl-propan-1-amine
EtOAc	ethyl acetate
GCMS	gas chromatography / mass spectrometry
HATU	*O*-(7-aza-1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HCl	hydrogen chloride
HOBt	1-hydroxybenzotriazole
HPLC	high pressure liquid chromatography
IPA	2-propanol
LDA	lithium diisopropylamide
m-CPBA	*meta*-chloroperoxybenzoic acid
LR	low resolution
LRMS	low resolution mass spectrometry
MeI	iodomethane
Me-THF	2-methyltetrahydrofuran

Me4-^{t}Bu-X-Phos	di-*tert*-butyl[3,4,5,6-tetramethyl-2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane
$MgSO_4$	magnesium sulfate
MP-$(OAc)_3BH$	solid supported (macro porous) triacetoxyborohydride
MPLC	medium pressure liquid chromatography
NaH	sodium hydride
Na_2SO_4	sodium sulfate
$NaBH_4$	sodium borohydride
$NaHCO_3$	sodium bicarbonate
NaOMe	sodium methoxide
NMO	4-methylmorpholine *N*-oxide
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$POCl_3$	phosphorus (V) oxychloride
PyBOP	(7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
SEM-Cl	2-(trimethylsilyl)ethoxymethyl chloride
SiliaCat® DPP-Pd	silica bound diphenylphosphine palladium (II)
TBAF	tetra-n-butylammonium fluoride
TBS-Cl	*tert*-butyldimethylsilyl chloride
t-BuOH	*tert*-butanol
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TPAP	tetra-n-propylammonium perruthenate (VII)
X-Phos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
HCOOH	formic acid
K*t*-OBu	potassium *tert*-butoxide
$Na_2S_2O_5$	sodium metabisulfite
NMR	nuclear magnetic resonance
TLC	thin layer chromatography
$(EtO)_2P(O)CH_2CN$	diethyl (cyanomethyl)phosphonate
MsCl	methanesulfonyl chloride
TsOH	*p*-toluenesulfonic acid
KCN	potassium cyanide
Si-DMT	silica supported dimercaptotriazine
TMS	trimethylsilane

CF_3TMS	(trifluoromethyl)trimethylsilane
PS-CDI	polystyrene supported 1,1'-carbonyldiimidazole

Alkyl Group Abbreviations

Me	methyl
Et	ethyl
n-Pr	normal propyl
i-Pr	isopropyl
n-Bu	normal butyl
i-Bu	isobutyl
s-Bu	secondary butyl
t-Bu	tertiary butyl
c-Pr	cyclopropyl
c-Bu	cyclobutyl
c-Pen	cyclopentyl
c-Hex	cyclohexyl

METHODS OF SYNTHESIS

The compounds of the present invention can be prepared according to the following general schemes using appropriate materials, and are further exemplified by the subsequent specific examples. The compounds illustrated in the examples are not to be construed as forming the only genus that is considered as the invention. The illustrative Examples below, therefore, are not limited by the compounds listed or by any particular substituents employed for illustrative purposes. Substituent numbering as shown in the schemes does not necessarily correlate to that used in the claims and often, for clarity, a single substituent is shown attached to the compound where multiple substituents are allowed under the definitions of the instant invention herein above.

Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:

All reactions were stirred (mechanically, stir bar/stir plate, or shaken) and conducted under an inert atmosphere of nitrogen or argon unless specifically stated otherwise.

All starting materials used to prepare the intermediates and final compounds described herein were obtained from commercial vendors, and were used as is upon receipt.

All temperatures are degrees Celsius (^{o}C) unless otherwise noted.

Ambient temperature is 15–25 °C.

Most compounds were purified by reverse-phase preparative HPLC, MPLC on silica gel, recrystallization and/or swish (suspension in a solvent followed by filtration of the solid).

The course of the reactions was followed by thin layer chromatography (TLC) and/or LCMS and/or NMR and reaction times are given for illustration only.

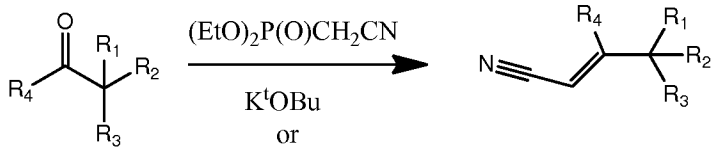
All end products were analyzed by NMR and LCMS.

Intermediates were analyzed by NMR and/or TLC and/or LCMS.

Method 1

General procedures to prepare intermediates of the instant invention are described in Scheme 1. Optionally substituted alkyl aldehydes or ketones I are condensed with diethyl (cyanomethyl)phosphonate in the presence of a suitable base, such as potassium *tert*-butoxide or triethylamine/LiBr to yield substituted acrylonitriles II used as intermediates in the synthesis of examples of the instant invention.

SCHEME 1

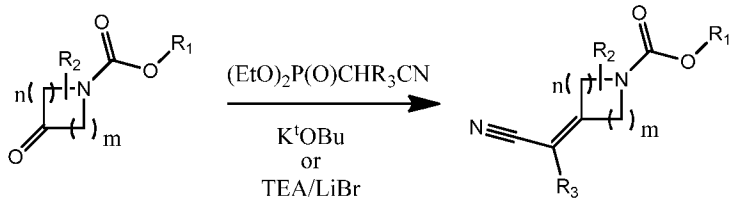


I II

Method 2

General procedures to prepare intermediates of the instant invention are described in Scheme 2. Optionally substituted carbamate protected heterocyclic ketones III are condensed with diethyl (cyanomethyl)phosphonate or another suitable cyanoalkylphosphonate in the presence of a suitable base, such as potassium *tert*-butoxide or TEA/LiBr, to yield optionally substituted acrylonitriles IV used as intermediates in the synthesis of examples of the instant invention.

SCHEME 2



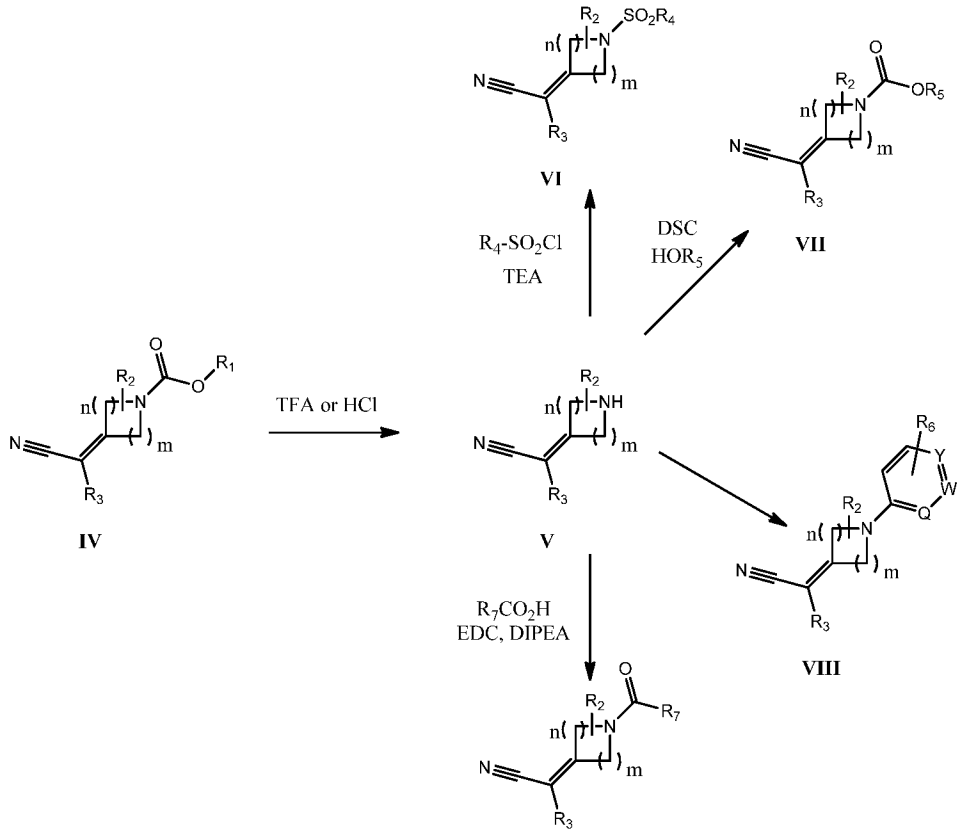
III IV

Method 3

General procedures to prepare intermediates of the instant invention are described in Scheme 3. Carbamate protected optionally substituted acrylonitriles IV are deprotected in the

presence of a suitable acid, such as TFA or HCl, to form amino intermediates V that are further derivatized to form sulfonamides VI, carbamates VII, *N*-arylated intermediates VIII, or amides IX. Sulfonamide derivatives VI are formed by reacting deprotected optionally substituted acrylonitriles with optionally substituted sulfonyl chlorides in a suitable solvent, such as DCM, using an appropriate base, such as DIPEA. Carbamate derivatives VII are formed by reacting deprotected optionally substituted acrylonitriles with a doubly activated carbonyl equivalent, such as DSC or triphosgene, and optionally substituted alcohols in the presence of a suitable base, such as TEA. Alternatively, carbamate derivatives VII may be prepared via reaction of the amine and an activated carbamoyl moiety such as an alkyl chloroformate in the presence of a suitable base, such as 2,6-lutidine, DIPEA or TEA, in a suitable solvent such as DCM. *N*-arylated derivatives VIII are formed by reacting deprotected optionally substituted acrylonitriles with optionally substituted electronically-deficient aryl halides using an appropriate base, such as TEA, in a solvent, such as DMF or NMP, at or around 120 °C. Amide derivatives IX are formed by reacting deprotected optionally substituted acrylonitriles with optionally substituted carboxylic acids in the presence of a suitable coupling agent such as EDC, CDI or HATU, in the presence of a suitable base such as TEA or Hunig's base. Alternatively, amide derivatives IX can be prepared in certain instances using an activated acylating reagent such as the acid chloride in place of the carboxylic acid.

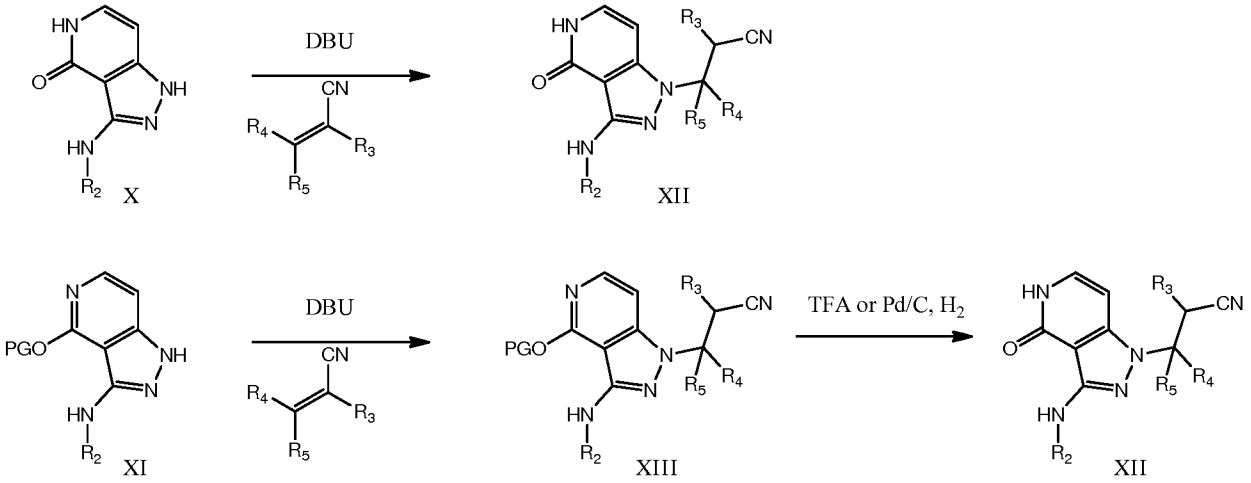
SCHEME 3



Method 4

General procedures to prepare intermediates of the instant invention are described in Scheme 4. Using an appropriate base, such as DBU, in a suitable solvent, such as MeCN, EtOH, *n*-BuOH or *tert*-BuOH, at a temperature between 25–110 °C either the unprotected pyrazolopyridone X or protected pyrazolopyridone XI can undergo conjugate addition to optionally substituted acrylonitriles to yield alkylated unprotected pyrazolopyridones XII or protected pyrazolopyridones XIII, an intermediate in the synthesis of examples of the instant invention. Deprotection of XIII to the free alkylated pyridone XII can then be effected either using a suitable acid, such as TFA, or under hydrogenolysis conditions using Pd on carbon at approximately 1 atmosphere of hydrogen, in a suitable solvent such as EtOAc, EtOH, MeOH, or using combinations of solvents thereof.

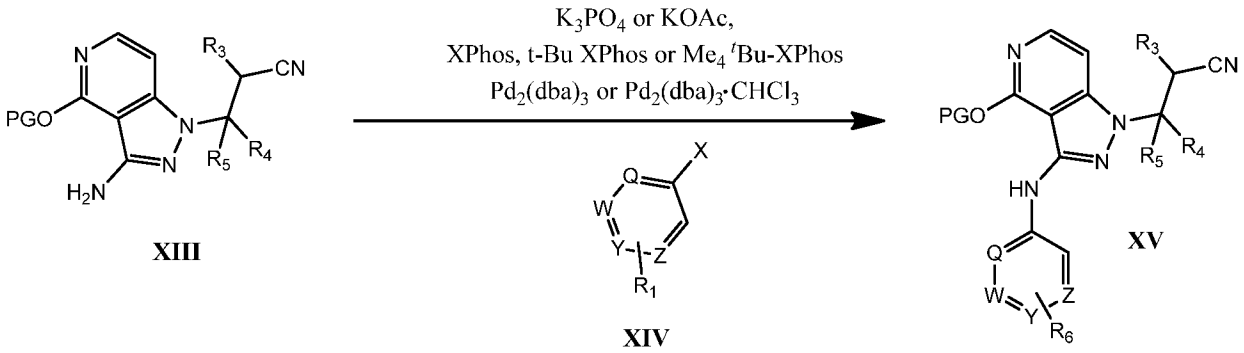
SCHEME 4



Method 5

General procedures to prepare examples of the instant invention are described in Scheme 5. Alkylated 3-amino pyrazolopyrimidines XIII (R_2 = H) are cross coupled to aryl and heteroaryl halides XIV using an appropriate catalytic palladium-ligand system, such as $Pd_2(dba)_3$ or $Pd_2(dba)_3 \cdot CHCl_3$, and 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (*t*-Bu XPhos) or di-*tert*-butyl[3,4,5,6-tetramethyl-2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane (Me_4 ^{t}Bu-XPhos), or 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos). Typical conditions employ 1–2 equivalents of the aryl/heteroaryl halide relative to the pyrazolopyrimidine with 10-25% Pd precatalyst loading, using an approximate Pd:ligand ratio of 1:2 to 1:2.5. Typically, the cross coupling is carried out using either 2-propanol or *t*-amyl alcohol solvents, and between 1–3.1 equivalents of KOAc or K_3PO_4 base. Reactions were typically carried out between 65–80°C, to yield intermediates XV of the instant invention.

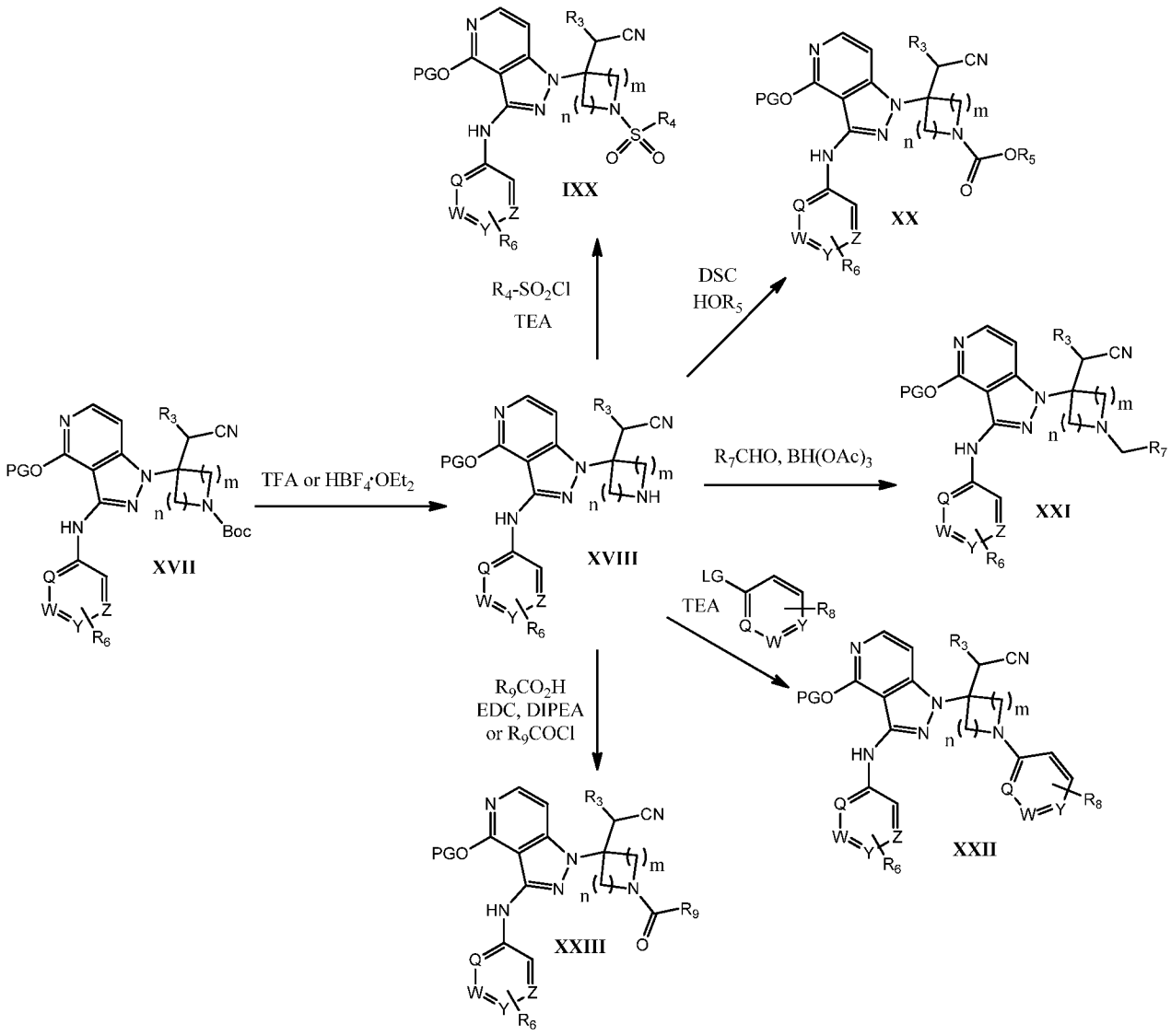
SCHEME 5



Method 6

General procedures to prepare examples of the instant invention are described in Scheme 6. Carbamate containing deprotected pyrazolopyridones XVII are deprotected in the presence of a suitable acid, such as TFA or $HBF_4{\cdot}OEt_2$, to form amino intermediates XVIII that are further derivatized to form sulfonamides IXX, carbamates XX, tertiary amines XXI, *N*-arylated intermediates XXII, or amides XXIII. Sulfonamide derivatives IXX are formed by reacting deprotected optionally substituted acrylonitriles with optionally substituted sulfonyl chlorides in a suitable solvent, such as DCM, using an appropriate base, such as DIPEA or TEA. Carbamate derivatives XX are formed by reacting deprotected optionally substituted acrylonitriles with a doubly activated carbonyl equivalent, such as DSC or triphosgene, and optionally substituted alcohols in the presence of a suitable base, such as DIPEA or TEA. Alternatively, carbamate derivatives XX may be prepared via reaction of the amine and an activated carbamoyl moiety such as an alkyl chloroformate in the presence of a suitable base, such as 2,6-lutidine, DIPEA or TEA, in a suitable solvent such as DCM. Tertiary amine derivatives XXI may be prepared via reaction of the amine an an appropriate carbonyl containing compound, such as an aldehyde or ketone, in the presence of a suitable acid catalyst such as TFA and a suitable reducing agent, such as sodium triacetoxyborohydride. *N*-arylated derivatives XXII are formed by reacting deprotected optionally substituted acrylonitriles with optionally substituted electronically-deficient aryl halides using an appropriate base, such as TEA, in a solvent, such as DMF or NMP, at or around 120 °C. Amide derivatives XXIII are formed by reacting deprotected optionally substituted acrylonitriles with optionally substituted carboxylic acids in the presence of a suitable coupling agent such as EDC, CDI or HATU, in the presence of a suitable base such as TEA or DIPEA. Alternatively, amide derivatives XXIII can be prepared in certain instances using an activated acylating reagent such as the acid chloride in place of the carboxylic acid.

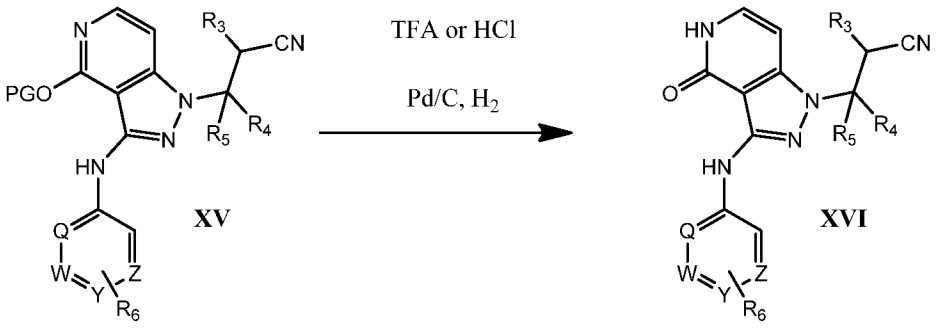
SCHEME 6



Method 7

General procedures to prepare examples of the instant invention are described in Scheme 7. Protected pyrazolopyrimidines XV are deprotected in the presence of acid, such as TFA or HCl, to afford the deprotected pyrazolopyridones XVI. Alternatively, in the case of hydrolytically unstable pyridone protecting groups (e.g. PG = Bn), deprotection could be achieved under hydrogenolysis conditions using Pd on Carbon in the presence of hydrogen in a suitable solvent such as EtOAc, EtOH, MeOH, or combinations of solvents thereof.

SCHEME 7

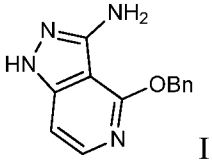


INTERMEDIATES

The following experimental procedures detail the preparation of chemical materials used in the synthesis of examples of the instant invention. The exemplified procedures are for illustrative purposes only, and are not intended to limit the scope of the instant invention in any way.

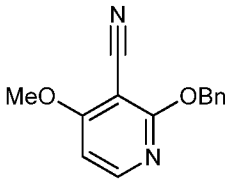
Intermediate 1

4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-3-amine



I-1

Step 1: 2-(benzyloxy)-4-methoxynicotinonitrile



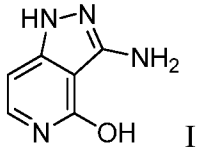
To a solution of 2-hydroxy-4-methoxynicotinonitrile (60 g, 0.4 mol) in toluene (0.60 L) was added Ag_2CO_3 (0.14 kg, 0.51 mol) and BnBr (87 g, 0.51 mol) at room temperature. The mixture was stirred at 50 °C for 3 hours. The mixture was filtered and the cake washed with DCM. The filtrate was concentrated *in vacuo* and petroleum ether (100 mL) was added to the residue and the solid was filtered to give 2-(benzyloxy)-4-methoxynicotinonitrile as a white solid. LRMS (ESI) calc'd for $C_{14}H_{13}N_2O_2$ $[M+H]^+$: 241, found 241. ^1H NMR (600 MHz $CDCl_3$): δ 8.21 (d, J = 6.6 Hz, 1H), 7.48 (d, J = 7.8 Hz, 2H), 7.38 (m, 2H), 7.32 (m, 1H), 6.58 (d, J = 6.0 Hz, 1H), 5.51 (s, 2H), 3.99 (s, 3H).

Step 2: 4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-3-amine

A suspension of 2-(benzyloxy)-4-methoxynicotinonitrile (100 g, 410 mmol) in hydrazine hydrate (0.20 kg, 4.1 mol) and *n*-BuOH (600 mL) was heated to reflux overnight. The mixture was concentrated *in vacuo* and purified by silica chromatography, eluting with 25% ethyl acetate in hexanes. Concentration of the desired fraction *in vacuo* afforded compound I-1. ^{1}H NMR (400 MHz $CDCl_3$) δ 9.97 (s, 1H), 7.75 (d, J = 6.4 Hz, 1H), 7.40 (d, J = 7.2 Hz, 2H), 7.24–7.33 (m, 3H), 6.69 (d, J = 6.4 Hz, 1H), 5.46 (s, 2H), 4.50 (s, 2H).

Intermediate 2

3-amino-1*H*-pyrazolo[4,3-*c*]pyridin-4-ol

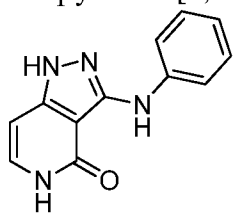


I-2

3-Cyano-2-hydroxy-4-methoxypyridine (1.00 g, 6.66 mmol) was dissolved in hydrazine hydrate (24.8 mL, 260 mmol) in a pressure vessel. The reaction mixture was heated to 140 °C for 21 hours, then cooled to ambient temperature and allowed to stir for an additional 48 hours. The reaction mixture was concentrated to give a tan solid that was slurried in diethyl ether, filtered, and washed with diethyl ether. The solid was dried under *vacuo* to give 3-amino-1*H*-pyrazolo[4,3-*c*]pyridin-4-ol, I-2. LRMS (ESI) calc'd for $C_6H_7N_4O$ $[M+H]^+$: 151, found 151.

Intermediate 3

3-(phenylamino)-1*H*-pyrazolo[4,3-*c*]pyridin-4(5*H*)-one



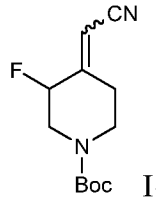
I-3

3-Amino-1*H*-pyrazolo[4,3-*c*]pyridin-4-ol (50.0 mg, 0.333 mmol), 2-di-*t*-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-tri-*i*-propylbiphenyl (4.0 mg, 8.3 μmol), Pd_2dba_3 (30.5 mg, 0.033 mmol), potassium phosphate tribasic (141 mg, 0.666 mmol), and bromobenzene (26 μL, 0.25 mmol) were suspended in 2-propanol (3.0 mL). The reaction mixture was sparged with argon for 10 minutes, then heated to 75 °C for 2 hours. The reaction mixture was diluted in 3:1 chloroform/isopropanol, washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by preparative reverse phase chromatography, eluting with acetonitrile/water with 0.1% TFA modifier. The fractions containing the desired product were combined and diluted in 3:1 chloroform/isopropanol, washed with aqueous sodium bicarbonate and brine. The combined aqueous layers were back extracted with 3:1 chloroform/isopropanol (× 1) and the combined organic layers were dried over Na_2SO_4, filtered

and concentrated *in vacuo* to give the desired product I-3 as a tan solid. LRMS (ESI) calc'd for $C_{12}H_{11}N_4O$ $[M+H]^+$: 227, found 227.

Intermediate 4-1

tert-butyl 4-(cyanomethylene)-3-fluoropiperidine-1-carboxylate

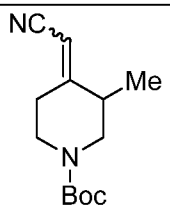


I-4-1

To a solution of diethyl (cyanomethyl)phosphonate (67 g, 0.38 mol) in THF (0.70 L) was added TEA (70 g, 0.69 mol) and LiBr (36 g, 0.42 mol) at room temperature. The reaction was stirred at room temperature for 30 minutes before *tert*-butyl-3-fluoro-4-oxopiperidine-1-carboxylate (75 g, 0.35 mol) was added. The reaction was stirred for another 3 hours, then H_2O (1.0 L) was added, and the mixture was extracted with EtOAc (× 3). The organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica chromatography, eluting with 10% ethyl acetate in hexanes. Concentration *in vacuo* of the desired fractions afforded the desired product as a white solid, I-4-1. ^{1}H NMR (600 MHz DMSO-*d6*): δ 5.88 (s, 1H), 5.27 (m, 0.5H), 5.19 (m, 0.5H), 3.86–3.40 (br m, 4H), 2.65 (m, 1H), 2.51 (m, 1H), 1.45 (s, 9H).

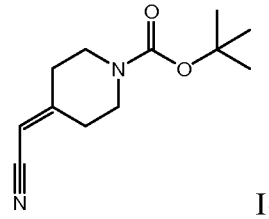
Following analogous procedure as described above for Intermediate 4-1, the following acrylonitrile intermediates shown in Table 1 were prepared:

Table 1

Intermediate #	Structure	Compound Name	^{1}H NMR / MS
I-4-2		*tert*-butyl 4-(cyanomethylene)-3-methylpiperidine-1-carboxylate	LRMS (ESI) calc'd for $C_8H_{13}N_2$ $[M-Boc+H]^+$: 137, found 137.

Intermediate 5-1

tert-butyl 4-(cyanomethylidene)piperidine-1-carboxylate

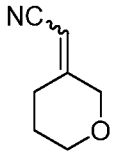
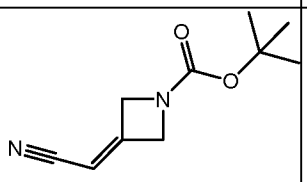
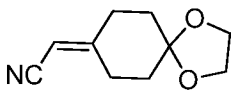


I-5-1

To a cooled, 0 °C solution of potassium *tert*-butoxide (263 mL, 263 mmol, 1.0 M in THF) and THF (200 mL), was slowly added diethyl (cyanomethyl)phosphonate (43.7 mL, 276 mmol). The reaction mixture was maintained at 0 °C for 10 minutes, then warmed to ambient temperature and maintained for 1 hour. The mixture was cooled to 0 °C and treated with the dropwise addition of *tert*-butyl 4-oxopiperidine-1-carboxylate (50.0 g, 251 mmol) in THF (150 mL) over 30 minutes. After addition, the mixture was maintained at 0 °C for 20 minutes, then warmed to ambient temperature and maintained for 18 hours. The reaction mixture was then diluted with water (800 mL) and extracted with EtOAc (× 2). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title compound as a light pink solid, I-5-1. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.19 (s, 1H), 3.48–3.53 (m, 4H), 2.56 (t, J = 5.4 Hz, 2H), 2.33 (t, J = 5.4 Hz, 2H), 1.47 (s, 9H).

Following an analogous procedure to that used for Intermediate I-5-1, the following acrylonitrile intermediates in Table 2 were prepared:

Table 2

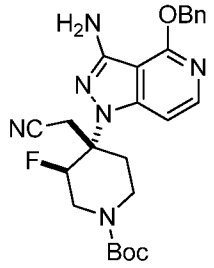
Intermediate #	Structure	Compound Name	^{1}H NMR / LRMS
I-5-2		2-(dihydro-2*H*-pyran-3(4*H*)-ylidene)acetonitrile	LRMS (ESI) calc'd for $C_7H_{10}NO$ $[M+H]^+$: 124, found 124.
I-5-3		*tert*-butyl 3-(cyanomethylidene)azetidine-1-carboxylate	^{1}H NMR (600 MHz, $CDCl_3$): δ 5.38–5.35 (m, 1H), 4.69 (m, 2H), 4.61–4.58 (m, 2H), 1.44 (s, 9H).
I-5-4		2-(1,4-dioxaspiro[4.5]decan-8-ylidene)acetonitrile	^{1}H NMR (600 MHz, $CDCl_3$): δ 5.11 (s, 1H), 3.97 (m, 4H),

			2.65 (t, J = 7.1 Hz, 2H), 2.42 (t, J = 7.1 Hz, 2H), 1.78 (t, J = 7.1 Hz, 2H), 1.75 (t, J = 7.1 Hz, 2H).

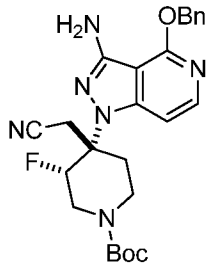
Intermediates 6-1 and 6-2

(3*R*,4*S* and 3*S*,4*R*)-*tert*-butyl 4-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)-3-fluoropiperidine-1-carboxylate (I-6-1), and

(3*S*,4*S* and 3*R*,4*R*)-*tert*-butyl 4-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)-3-fluoropiperidine-1-carboxylate (I-6-2)



I-6-1



I-6-2

To a solution of *tert*-butyl 4-(cyanomethylene)-3-fluoropiperidine-1-carboxylate (50 g, 208 mmol) and 4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-3-amine (25 g, 104 mmol) in CH_3CN (200 mL) at room temperature, was added DBU (17.4 g, 115 mmol). The mixture was stirred at 50 °C for 48 hours before being concentrated *in vacuo*. Water (200 mL) was then added and the reaction was extracted with EtOAc (×3). The organic layer was washed with brine (500 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica chromatography, eluting with 9–33% EtOAc in hexanes to afford the two diastereomers as white solids.

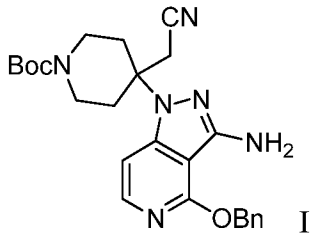
Major isomer I-6-1: LRMS (ESI) calc'd for $C_{25}H_{30}N_6O_3F$ $[M+H]^+$: 481, found 481. ^1H NMR (600 MHz, DMSO-*d6*): δ 7.77 (d, J = 6.1 Hz, 1H), 7.48 (d, J = 6.5 Hz, 2H), 7.35 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.17 (d, J = 6.1 Hz, 1H), 5.51 (s, 2H), 5.47 (m, 1H), 5.30 (s, 2H), 4.13 (t, J = 13.1 Hz, 1H), 3.91 (d, J = 13.1 Hz, 1H), 3.17 (m, 2H), 3.15 (m, 1H), 2.91 (br m, 1H), 2.75 (d, J = 15.5 Hz, 1H), 2.05 (t, J = 13.0 Hz, 1H), 1.37 (s, 9H). SFC separation was achieved using a ChiralPak OJ-H, with 30% methanol modifier in CO_2: retention times = 3.71 (I-6-1A) & 5.73 (I-6-1B) minutes.

Minor isomer I-6-2: LRMS (ESI) calc'd for $C_{25}H_{30}N_6O_3F$ $[M+H]^+$: 481, found 481. ^1H NMR (600 MHz, DMSO-*d6*): δ 7.77 (d, J = 7.0 Hz, 1H), 7.55 (d, J = 7.0 Hz, 2H), 7.43 (t, J = 8.2 Hz, 2H), 7.36 (t, J = 7.3 Hz, 1H), 7.25 (d, J = 6.7 Hz, 1H), 5.56 (s, 2H), 5.49 (s, 2H), 5.23 (d, J =

46.8 Hz, 1H), 4.18 (m, 2H), 3.57 (d, J = 17.2 Hz, 1H), 3.46 (d, J = 17.3 Hz, 1H), 3.35–3.14 (m, 2H), 2.67 (m, 1H), 2.44 (m, 1H), 1.38 (s, 9H). SFC separation was achieved using a ChiralPak AD-3, with 5–40% ethanol modifier (0.05% DEA in ethanol) in CO_2: retention times = 5.40 (I-6-2A) & 6.12 (I-6-2B) minutes.

Intermediate 7

tert-butyl 4-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate

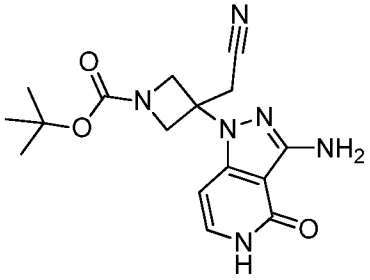


I-7

To a solution of 4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-3-amine (155 g, 645 mmol) in CH_3CN (2.50 L), was added (batchwise) *tert*-butyl 4-(cyanomethylidene)piperidine-1-carboxylate (286 g, 1.29 mol) followed by dropwise addition of DBU (99.0 g, 650 mmol) at 20 °C over 20 minutes. The resulting solution was stirred for 3 days at 20 °C, concentrated *in vacuo* at 40–45 °C, and then purified by silica chromatography, eluting with 0–50% ethyl acetate/petroleum ether. Concentration of the desired fraction *in vacuo* afforded compound I-7. LRMS (ESI) calc'd for $C_{25}H_{31}N_6O_3$ $[M+H]^+$: 463, found 463. ^1H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, 1H), 7.34–7.50 (m, 5H), 6.84 (d, 1H), 5.54 (s, 2H), 4.51 (br s, 2H), 3.94–3.97 (d, 2H), 3.05 (br s, 2H), 2.85–2.90 (m, 2H), 2.79 (s, 2H), 1.92–2.04 (m, 2H), 1.45 (s, 9H).

Intermediate 8

tert-butyl 3-(3-amino-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-3-(cyanomethyl)azetidine-1-carboxylate



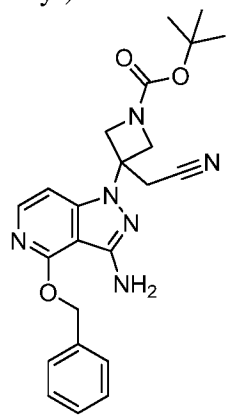
I-8

To a solution of 3-amino-1*H*-pyrazolo[4,3-*c*]pyridin-4-ol (500 mg, 3.33 mmol) and *tert*-butyl 3-(cyanomethylidene)azetidine-1-carboxylate (356 mg, 1.83 mmol) in DMF (22.2 mL) was added DBU (0.602 mL, 4.00 mmol). The reaction was heated to 50 °C and allowed to stir for 1 hour, after which a second portion of *tert*-butyl 3-(cyanomethylidene)azetidine-1-

carboxylate (356 mg, 1.83 mmol) was added to the reaction mixture. After an additional 2 hours at 50 °C the reaction was cooled, diluted with water (100 mL) and extracted with 3:1 $CHCl_3$:IPA (× 3). The combined organic layers were washed once with brine (50 mL). The resulting organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by reverse phase chromatography, eluting with acetonitrile/water with 0.1% TFA modifier. Fractions containing desired product were diluted with EtOAc, washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford compound I-8. LRMS (ESI) calc'd for $C_{16}H_{21}N_6O_3$ $[M+H]^+$: 345, found 345. ^1H NMR (600 MHz, DMSO-*d6*): δ 10.92 (s, 1H), 7.07 (t, *J* = 5.7 Hz, 1H), 6.20 (d, *J* = 7.2 Hz, 1H), 5.46 (s, 2H), 4.35 (m, 2H), 4.15 (m, 2H), 3.28 (s, 2H) 1.34 (s, 9H).

Intermediate 9

tert-butyl 3-[3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]-3-(cyanomethyl)azetidine-1-carboxylate

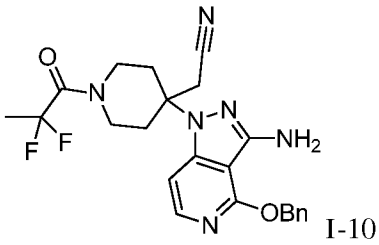


I-9

4-(Benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-3-amine (8.0 g, 33 mmol) and *tert*-butyl 3-(cyanomethylidene)azetidine-1-carboxylate (9.7 g, 50 mmol) were dissolved in acetonitrile (200 mL) and DBU (7.6 g, 50 mmol) was added. The resulting mixture was stirred for 2 hours at room temperature, then concentrated *in vacuo* and purified by silica chromatrography, eluting with 17–67% EtOAc in hexanes. Concentration of the desired fractions afforded compound I-9, as a white solid. LRMS (ESI) calc'd for $C_{23}H_{27}N_6O_3$ $[M+H]^+$: 435, found 435. ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 6.4 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.30–7.39 (m, 3H), 6.65 (d, *J* = 6.4 Hz, 1H), 5.51 (s, 2H), 4.60 (d, *J* = 9.2 Hz, 2H), 4.52 (s, 2H), 4.22 (d, *J* = 9.6 Hz, 2H), 3.04 (s, 2H), 1.44 (s, 9H).

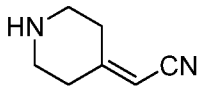
Intermediate 10

2-(4-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1-(2,2-difluoropropanoyl)piperidin-4-yl)acetonitrile



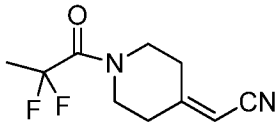
I-10

Step 1: 2-(piperidin-4-ylidene)acetonitrile HCl salt



To *tert*-butyl 4-(cyanomethylene)piperidine-1-carboxylate (2.03 g, 9.15 mmol) was added HCl in dioxane (21 mL, 84 mmol, 4M) and the resulting slurry was stirred at room temperature for 30 minutes, then concentrated *in vacuo* to afford a crude product that was used as is without further purification. ^{1}H NMR (600 MHz, DMSO-*d6*): δ 9.30 (br s, 1H), 5.66 (s, 1H), 3.20–3.10 (m, 4H), 2.67 (t, *J* = 6.1 Hz, 2H), 2.56 (t, *J* = 6.1 Hz, 2H).

Step 2: 2-(1-(2,2-difluoropropanoyl)piperidin-4-ylidene)acetonitrile



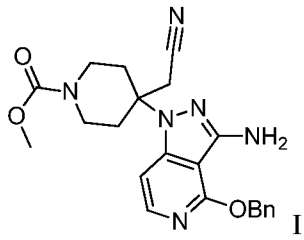
To the mixture of 2-(piperidin-4-ylidene)acetonitrile (1.12 g, 9.15 mmol), HATU (5.22 g, 13.7 mmol) in DCM (36.6 mL), was added DIPEA (8.0 mL, 46 mmol) and 2,2-difluoropropanoic acid (2.00 g, 18.3 mmol). The reaction mixture was stirred at room temperature for 2 hours and then concentrated *in vacuo* to afford a residue that was purified by silica chromatography, eluting with 3% EtOAc in hexanes. Concentration of the desired fraction afforded 2-(1-(2,2-difluoropropanoyl)piperidin-4-ylidene)acetonitrile as a white solid. LRMS (ESI) calc'd for $C_{10}H_{13}F_2N_2O$ [M+H]+: 215, found 215. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.23 (s, 1H), 3.73–3.75 (m, 4H), 2.62–2.63 (m, 2H), 2.41 (q, *J* = 6.2 Hz, 2H), 1.84 (t, *J* = 19.9 Hz, 3H).

Step 3: 2-(4-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1-(2,2-difluoropropanoyl)piperidin-4-yl)acetonitrile

To a solution of 4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-3-amine (4.76 g, 19.8 mmol) in acetonitrile (45 mL) was added 2-(1-(2,2-difluoropropanoyl)piperidin-4-ylidene)acetonitrile (2.12 g, 9.90 mmol) and DBU (1.49 mL, 9.90 mmol). The reaction mixture was stirred at 40 °C for 72 hours, then concentrated *in vacuo* to afford a residue that was purified by silica chromatography, eluting with 43% EtOAc in hexanes. LRMS (ESI) calc'd for $C_{23}H_{25}F_2N_6O_2$ $[M+H]^+$: 455, found 455. ^{1}H NMR (600 MHz, DMSO-*d6*): δ 7.76 (d, *J* = 6.4 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.20 (d, *J* = 6.3 Hz, 1H), 5.52 (s, 2H), 5.46 (s, 2H), 4.12 (m, 1H), 4.01 (m, 1H), 3.31 (m, 1H), 3.17 (s, 2H), 3.01 (m, 1H), 2.83–2.77 (m, 2H), 2.04–1.94 (m, 2H), 1.79 (t, *J* = 20.1 Hz, 3H).

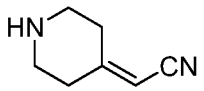
Intermediate 11

methyl 4-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate



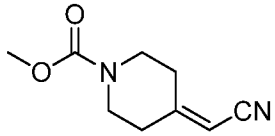
I-11

Step 1: 2-(piperidin-4-ylidene)acetonitrile TFA salt



To a solution of *tert*-butyl 4-(cyanomethylidene)piperidine-1-carboxylate (3.00 g, 13.5 mmol) in dichloromethane (30 mL) at 20 °C, was added trifluoroacetic acid (13.0 g, 115 mmol). The resulting solution was stirred for 1 hour at 20 °C and then concentrated *in vacuo* to afford an off-white oil that was used as is.

Step 2: methyl 4-(cyanomethylene)piperidine-1-carboxylate



To a solution of crude 2-(piperidin-4-ylidene)acetonitrile TFA salt (3.00 g, 13.7 mmol) in dichloromethane (30 mL), was added triethylamine (7.50 g, 74.1 mmol) and chloro(methoxy)methanone (2.80 g, 29.6 mmol). The resulting solution was stirred for 30 minutes at 20 °C and then concentrated *in vacuo*. The residue was purified by silica chromatography, eluting with 25% EtOAc in hexanes. Concentration of the desired fractions afforded methyl 4-(cyanomethylidene)piperidine-1-carboxylate as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.22 (s, 1H), 3.74 (s, 3H), 3.57 (m, 4H), 2.59 (t, J = 2.8 Hz, 2H), 2.36 (t, J = 2.8 Hz, 2H).

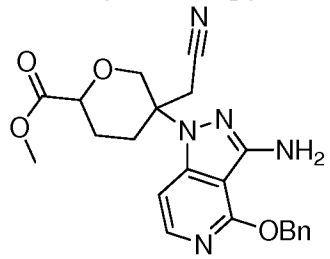
Step 3: methyl 4-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate

To a solution of 4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-3-amine (1.00 g, 4.16 mmol) in ethanol (10 mL), was added methyl 4-(cyanomethylidene)piperidine-1-carboxylate (750 mg, 4.16 mmol) and DBU (630 mg, 4.14 mmol). The resulting solution was stirred for 8 hours at 78 °C. The reaction mixture was concentrated *in vacuo* and purified by silica

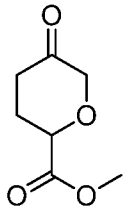
chromatrography, eluting with 50% EtOAc in hexanes and then the desired fractions were concentrated *in vacuo* and repurified by preparative TLC using DCM/MeOH=10:1 to afford compound I-11 as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 6.4 Hz, 1H), 7.50 (d, J = 7.2 Hz, 2H), 7.36–7.44 (m, 3H), 6.86 (d, J = 6.4 Hz, 1H), 5.57 (s, 2H), 4.53 (br, 2H), 4.12 (br, 2H), 3.72 (s, 3H), 3.05–3.17 (m, 2H), 2.90–2.98 (m, 2H), 2.82 (s, 2H), 1.96–2.05 (m, 2H).

Intermediate 12

methyl 5-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-5-(cyanomethyl)tetrahydro-2*H*-pyran-2-carboxylate

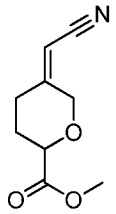


Step 1: methyl 5-oxotetrahydro-2*H*-pyran-2-carboxylate



To a solution of methyl 5-hydroxy-tetrahydro-2*H*-pyran-2-carboxylate (487 mg, 3.04 mmol) in CH_2Cl_2 (10 mL), was added Dess–Martin periodinane (1.60 g, 3.80 mmol). The reaction was stirred at room temperature for 2 hours, then diluted with saturated sodium thiosulfate solution and saturated sodium bicarbonate solution and filtered through Celite. The aqueous layer was extracted with CH_2Cl_2 (× 2) and the combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a residue that was purified by silica chromatography, eluting with 33% EtOAc in hexanes. Concentration of the desired fractions afforded methyl 5-oxotetrahydro-2*H*-pyran-2-carboxylate as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.40 (dd, J = 9.2, 4.9 Hz, 1H), 4.32 (d, J = 16.9 Hz, 1H), 4.05 (d, J = 16.9 Hz, 1H), 3.79 (s, 3H), 2.56 (m, 2H), 2.39 (m, 1H), 2.21 (m, 1H).

Step 2: methyl 5-(cyanomethylene)tetrahydro-2*H*-pyran-2-carboxylate



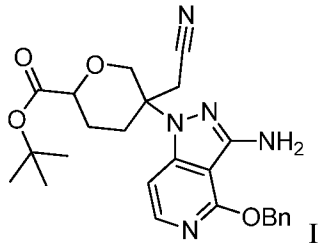
A mixture of triethylamine (594 μL, 4.26 mmol), lithium brimide (341 mg, 3.93 mmol) and diethyl (cyanomethyl)phosphonate (379 μL, 2.34 mmol) in THF (5 mL) was stirred for 30 minutes at room temperature. Methyl 5-oxotetrahydro-2*H*-pyran-2-carboxylate(337 mg, 2.13 mmol) in THF (1 mL) was then added and the reaction mixture was stirred for 12 hours before being quenched with water (5 mL) and extracted with ethyl acetate (× 4). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a residue that was purified by silica chromatography, eluting with 38% EtOAc in hexanes. Concentration of the desired fractions afforded methyl 5-(cyanomethylene)tetrahydro-2*H*-pyran-2-carboxylate (*E* and *Z* = 5:3) as a colorless oil. LRMS (ESI) calc'd for $C_9H_{12}NO_3$ $[M+H]^+$: 182, found 182. ^{1}H NMR (600 MHz, DMSO-*d6*): δ 5.62 (d, *J* = 16.7 Hz, 1H), 4.46 (d, *J* = 13.7 Hz, 0.5H), 4.29 (m, 1.5H), 4.16 (d, *J* = 13.7 Hz, 0.5H), 4.09 (d, *J* = 13.4 Hz, 0.5H), 3.63 (d, *J* = 1.4 Hz, 3H), 2.68 (dt, *J* = 14.7, 4.5 Hz, 0.5H), 2.52 (m, 1.5H), 2.02 (m, 1H), 1.69 (m, 1H).

Step 3: 5-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-5-(cyanomethyl)tetrahydro-2*H*-pyran-2-carboxylate

To 4-(benzyloxy)-1*H*-pyrazolo[4,3-c]pyridin-3-amine (1.56 g, 6.46 mmol) in acetonitrile (4.3 mL) was added methyl 5-(cyanomethylene)tetrahydro-2*H*-pyran-2-carboxylate(234 mg, 1.29 mmol) and DBU (195 μL, 1.29 mmol). The reaction mixture was stirred at 40 °C for 72 hours, then concentrated *in vacuo* to afford a residue that was purified by silica chromatography, eluting with 33% EtOAc in hexanes. Concentration of the desired fractions afforded compound I-12 as a yellow solid. LRMS (ESI) calc'd for $C_{22}H_{24}N_5O_4$ $[M+H]^+$: 422, found 422. ^{1}H NMR (600 MHz, DMSO-*d6*): δ 7.70 (d, *J* = 6.4 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.17 (d, *J* = 6.4 Hz, 1H), 5.48 (s, 2H), 5.40 (s, 2H), 4.29 (dd, *J* = 9.4, 3.9 Hz, 1H), 4.19 (d, *J* = 12.0 Hz, 1H), 4.05 (d, *J* = 11.7 Hz, 1H), 3.66 (s, 3H), 3.32 (m, 1H), 3.28 (d, *J* = 9.1 Hz, 1H), 2.55 (m, 1H), 2.49–2.44 (m, 1H), 1.94–1.78 (m, 2H).

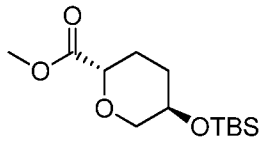
Intermediate 13

tert-butyl 5-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-5-(cyanomethyl)tetrahydro-2*H*-pyran-2-carboxylate



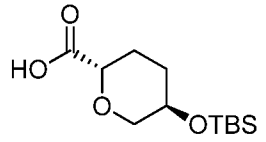
I-13

Step 1: (2*S*,5*R*)-methyl 5-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-carboxylate



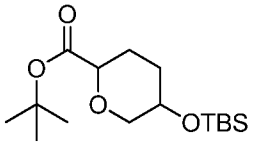
To a solution of (2*S*,5*R*)-methyl 5-hydroxytetrahydro-2*H*-pyran-2-carboxylate (3.48 g, 21.7 mmol) in CH_2Cl_2 (90 mL) was added imidazole (2.22 g, 32.6 mmol) and *tert*-butyldimethylsilyl chloride (3.93 g, 26.1 mmol). The reaction mixture was stirred at room temperature overnight, then quenched with water (50 mL) and extracted with CH_2Cl_2 (× 3). The combined organic layers were concentrated *in vacuo* to afford a residue that was purified by silica chromatography, eluting with 10% EtOAc in hexanes. Concentration of the desired fractions afforded (2*S*,5*R*)-methyl 5-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-carboxylate as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.97 (ddd, *J* = 11.0, 4.9, 1.9 Hz, 1H), 3.90 (dd, *J* = 11.6, 2.2 Hz, 1H), 3.74 (s, 3H), 3.61 (m, 1H), 3.13 (dd, *J* = 11.0, 9.8 Hz, 1H), 2.06 (m, 2H), 1.68–1.60 (m, 1H), 1.51–1.45 (m, 1H), 0.85 (s, 9H), 0.03 (d, *J* = 6.45 Hz, 6H).

Step 2: (2*S*,5*R*)-5-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-carboxylic acid



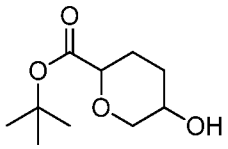
To the solution of (2*S*,5*R*)-methyl 5-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-carboxylate (5.40 g, 19.7 mmol) in methanol (55 mL) was added 4N aqeuous potassium hydroxide (24.6 mL, 98.4 mmol). The reaction mixture was stirred at room temperature for 2 hours and then the solvent was removed *in vacuo*. The aqueous residue was acidified to pH~2 using 1N HCl and extracted with chloroform/isopropanol (3:1, × 3) . The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford (2*S*,5*R*)-5-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-carboxylic acid as a white solid. LRMS (ESI) calc'd for $C_{12}H_{25}O_4Si$ $[M+H]^+$: 261, found 261. ^{1}H NMR (600 MHz, DMSO-*d6*): δ 12.56 (s, 1H), 3.78 (dd, *J* = 11.1, 2.9 Hz, 1H), 3.73 (m, 1H), 3.58 (m, 1H), 3.03 (dd, *J* = 10.8, 9.5 Hz, 1H), 1.90 (m, 2H), 1.48–1.40 (m, 2H), 0.81 (s, 9H), 0.05 (d, *J* = 4.1 Hz, 6H).

Step 3: (2*S*,5*R*)-*tert*-butyl 5-((tert-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-carboxylate



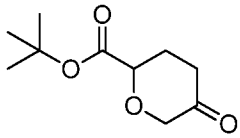
To a solution of (2*S*,5*R*)-5-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-carboxylic acid (5.46 g, 19.8 mmol) in toluene (80 mL) at 95 °C was added 5 mL of a solution of *N,N*-dimethylformamide di-*tert*-butyl acetal (19.0 mL, 79 mmol) in toluene (10 mL) under nitrogen. The resulting solution was stirred at 95 °C for 1 hour, at which point the remaining acetal solution was added and the resulting solution was stirred for another 1 hour. The reaction was then concentrated *in vacuo* to afford a residue that was purified by silica chromatography, eluting with 10% EtOAc in hexanes. Concentration of the desired fractions afforded (2*S*,5*R*)-*tert*-butyl 5-((tert-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-carboxylate as a colorless oil. LRMS (ESI) calc'd for $C_{16}H_{33}O_4Si$ $[M+H]^+$: 317, found 317. ^1H NMR (600 MHz, DMSO-*d6*) δ 3.74 (m, 2H), 3.59 (tt, *J* = 9.7, 4.6 Hz, 1H), 3.02 (dd, *J* = 10.8, 9.5 Hz, 1H), 1.90–1.81 (m, 2H), 1.50–1.41 (m, 2H), 1.38 (s, 9H), 0.81 (s, 9H), 0.02 (d, *J* = 4.7 Hz, 6H).

Step 4: *tert*-butyl 5-hydroxytetrahydro-2*H*-pyran-2-carboxylate



To *tert*-butyl 5-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-carboxylate (4.58 g, 14.5 mmol) was added tetra-*n*-butylammonium fluoride (72.0 mL, 72.0 mmol, 1M in THF) and the reaction was stirred at room temperature for 2 hours, then concentrated *in vacuo* to afford a residue that was purified by silica chromatography, eluting with 44% EtOAc in hexanes. Concentration of the desired fraction afforded *tert*-butyl 5-hydroxytetrahydro-2*H*-pyran-2-carboxylate. LRMS (ESI) calc'd for $C_{10}H_{19}O_4$ $[M+H]^+$: 203, found 203. ^1H NMR (600 MHz, DMSO-*d6*): δ 4.79 (d, *J* = 4.8 Hz, 1H), 3.77 (ddd, *J* = 10.7, 4.7, 1.9 Hz, 1H), 3.71 (dd, *J* = 10.9, 2.6 Hz, 1H), 3.40–3.34 (m, 1H), 2.96 (t, *J* = 10.2 Hz, 1H), 1.83 (m, 2H), 1.36 (s, 9H), 1.48–1.13 (m, 2H).

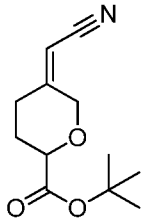
Step 5: *tert*-butyl 5-oxotetrahydro-2*H*-pyran-2-carboxylate



To a solution of *tert*-butyl 5-hydroxytetrahydro-2*H*-pyran-2-carboxylate (2.85 g, 14.1 mmol) in CH_2Cl_2 (45 mL) was added Dess–Martin periodinane (7.47 g, 17.6 mmol). The

reaction was stirred at room temperature for 2 hours, then diluted with saturated sodium thiosulfate and saturated sodium bicarbonate solution. The aqueous layer was extracted with CH_2Cl_2 (× 4), and the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a residue that was purified by silica chromatography, eluting with 25% EtOAc in hexanes. Concentration of the desired fractions afforded *tert*-butyl 5-oxotetrahydro-2*H*-pyran-2-carboxylate as a yellow oil. ^{1}H NMR (600 MHz, DMSO-*d6*): δ 4.31 (dd, *J* = 9.5, 4.6 Hz, 1H), 4.05 (d, *J* = 16.5 Hz, 2H), 2.75 (dt, *J* = 16.8, 5.3 Hz, 1H), 2.37 (dt, *J* = 16.8, 5.3 Hz, 1H), 2.24–2.08 (m, 1H), 1.98 (m, 1H), 1.38 (s, 9H).

Step 6: <u>*tert*-butyl 5-(cyanomethylene)tetrahydro-2*H*-pyran-2-carboxylate</u>



A mixture of triethylamine (3.56 mL, 25.6 mmol), lithium bromide (2.05 g, 23.7 mmol) and diethyl (cyanomethyl)phosphonate (2.28 mL, 14.1 mmol) in THF (40 mL) was stirred for 30 minutes at room temperature before *tert*-butyl 5-oxotetrahydro-2*H*-pyran-2-carboxylate (2.56 g, 12.8 mmol) in THF (10 mL) was added. The reaction was stirred at room temperature overnight, quenched with water (20 mL), and extracted with ethyl acetate (× 4). The combined organic layers was dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a residue that was purified by silica chromatography, eluting with 25% EtOAc in hexanes. Concentration of the desired fractions afforded *tert*-butyl 5-(cyanomethylene)tetrahydro-2*H*-pyran-2-carboxylate as a white solid and as a 9:7 mixture of *E* and *Z* isomers. LRMS (ESI) calc'd for $C_{12}H_{18}NO_3$ $[M+H]^+$: 224, found 224. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 5.61 (d, *J* = 14.9 Hz, 1H), 4.46 (d, *J* = 14.1 Hz, 0.5H), 4.28 (d, *J* = 13.5 Hz, 0.5H), 4.12 (m, 1.5H), 4.06 (d, *J* = 13.4 Hz, 0.5H), 2.70–2.64 (m, 0.5 H), 2.66–2.53 (m, 1.5H), 2.05–1.96 (m, 1H), 1.68–1.63 (m, 1H), 1.38 (s, 9H).

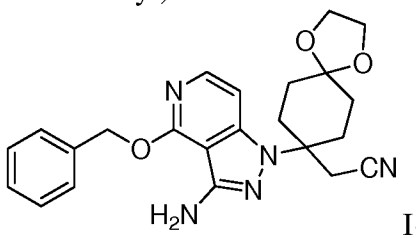
Step 7: <u>*tert*-butyl 5-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-5-(cyanomethyl)tetrahydro-2*H*-pyran-2-carboxylate</u>

To a solution of 4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-3-amine (10.8 g, 45.0 mmol) in acetonitrile (35mL) was added *tert*-butyl 5-(cyanomethylene)tetrahydro-2*H*-pyran-2-carboxylate (2.00 g, 8.96 mmol) and DBU (1.35 mL, 8.96 mmol). The vial was sealed and stirred at 40 °C for 72 hours, then concentrated *in vacuo* to afford a residue that was purified by silica chromatography, eluting with 43% EtOAc in hexanes. Concentration of the desired fractions afforded *tert*-butyl 5-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-5-(cyanomethyl)tetrahydro-2*H*-pyran-2-carboxylate (Distereomer 1 and 2 = 3:1), both as light

yellow solids. Diastereomer I-13-1: LRMS (ESI) calc'd for $C_{25}H_{30}N_5O_4$ $[M+H]^+$: 464, found 464. ^1H NMR (600 MHz, DMSO-*d6*): δ 7.70 (d, *J* = 6.5 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 6.5 Hz, 1H), 5.48 (s, 2H), 5.40 (bs, 2H), 4.21 (d, *J* = 11.9 Hz, 1H), 4.11 (dd, *J* = 9.1, 3.7 Hz, 1H), 4.02 (d, *J* = 12.1 Hz, 1H), 3.23 (d, *J* = 4.5 Hz, 2H), 2.45–2.38 (m, 2H), 1.86–1.75 (m, 2H), 1.38 (s, 9H). Diastereomer I-13-2: LRMS (ESI) calc'd for $C_{25}H_{30}N_5O_4$ $[M+H]^+$: 464, found 464. ^1H NMR (600 MHz, DMSO-*d6*): δ 7.71 (d, *J* = 6.4 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 6.4 Hz, 1H), 5.48 (s, 2H), 5.40 (br s, 2H), 4.68 (d, *J* = 14.6 Hz, 1H), 4.15 (dd, *J* = 10.6, 2.9 Hz, 1H), 3.75–3.68 (d, *J* = 12.9 Hz, 1H), 3.00 (d, *J* = 3.9 Hz, 2H), 2.80 (d, *J* = 11.7 Hz, 1H), 2.05–1.95 (m, 1H), 1.85–1.80 (m, 1H), 1.55–1.48 (m, 1H), 1.32 (s, 9H). SFC separation of Diastereomer I-13-1 was performed by Chiralpak IA column 21 × 250 mm, eluting with 30% methanol in CO_2 to afford Enantiomer 1 (3.06 minutes – I-13-1A) and Enantiomer 2 (4.41 minutes – I-13-1B).

Intermediate 14

2-(8-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1,4-dioxaspiro[4.5]decan-8-yl)acetonitrile

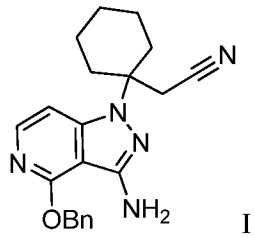


I-14

To a suspension of 4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-3-amine (1.0 g, 4.2 mmol) in MeCN (10 mL) was added 2-(1,4-dioxaspiro[4.5]decan-8-ylidene)acetonitrile (7.5 g, 42 mmol) and DBU (1.3 g, 8.3 mmol). The resulting reaction mixture was stirred at 55 °C for 41 hours. The reaction mixture volume was reduced by half *in vacuo* then purified by silica chromatography, eluting with 0–100 EtOAc in hexanes to give compound I-14. LRMS (ESI) calc'd for $C_{23}H_{26}N_5O_3$ $[M+H]^+$: 420, found 420. ^1H NMR (600 MHz, DMSO-*d6*): δ 7.70 (d, *J* = 6.4, 1H), 7.47 (d, *J* = 7.5, 2H), 7.35 (t, *J* = 7.5, 2H), 7.28 (t, *J* = 7.3, 1H), 7.09 (d, *J* = 6.4, 1H), 5.47 (s, 2H), 5.38 (s, 2H), 3.88–3.83 (m, 2H), 3.83–3.78 (m, 2H), 3.03 (s, 2H), 2.71 (d, *J* = 13.9, 2H), 2.03–1.89 (m, 2H), 1.70–1.59 (m, 2H), 1.53–1.41 (m, 2H).

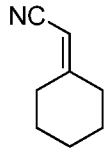
Intermediate 15

2-(1-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile



I-15

Step 1: 2-cyclohexylideneacetonitrile



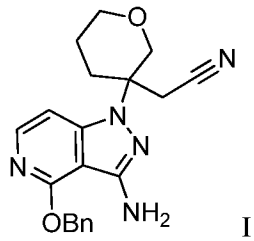
A solution of potassium hydroxide (2.86 g, 51.1 mmol) in acetonitrile (30 mL) was stirred at 80 °C for 5 minutes before a solution of cyclohexanone (5.00 g, 51.0 mmol) in acetonitrile (10 mL) was added dropwise. The resulting solution was stirred for 2 hours at 80 °C and then concentrated *in vacuo*. The residue was purified by silica chromatography, eluting with 0–1% EtOAc in hexanes to afford 2-cyclohexylideneacetonitrile as a colorless oil. LR GCMS (EI) calc'd for $C_8H_{11}N$ $[M]^+$: 121, found 121.

Step 2: 2-(1-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile

To 4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-3-amine (0.050 g, 0.21 mmol) and 2-cyclohexylideneacetonitrile (0.050 g, 0.42 mmol) in ethanol (0.1 mL) was added DBU (0.031 g, 0.20 mmol). The resulting solution was stirred for 16 hours at 55 °C, then concentrated *in vacuo* to afford crude compound I-15 as a yellow solid. LRMS (ESI) calc'd for $C_{21}H_{24}N_5O$ $[M+H]^+$: 362, found 362.

Intermediate 16-1

2-(3-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-3-yl)acetonitrile



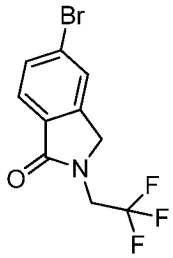
I-16

To 4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-3-amine (500 mg, 2.08 mmol) in acetonitrile (6.9 mL) was added (*E*)-2-(dihydro-2*H*-pyran-3(4*H*)-ylidene)acetonitrile (436 mg, 3.54 mmol) and DBU (314 μL, 2.08 mmol). The flask was sealed and heated to 40°C for 24 hours, then concentrated *in vacuo* and purified by silica chromatography, eluting with 10–100% EtOAc in hexanes. The product was collected and concentrated *in vacuo* to afford the desired

product as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.81 (d, J = 6.4 Hz, 1H), 7.48 (d, J = 7.3 Hz, 2H), 7.40 (apparent t, J = 6.9 Hz, 2H), 7.35 (m, 1H), 7.00 (d, J = 6.9 Hz, 1H), 5.53 (s, 2H), 4.49 (s, 2H), 4.21 (d, J = 12.1 Hz, 1H), 4.08 (d, J = 12.1 Hz, 1H), 3.82 (m, 1H), 3.69 (m, 1H), 3.09 (d, J = 18.5 Hz, 1H), 3.01 (d, J = 18.5 Hz, 1H), 2.65 (m, 1H), 2.46 (m, 1H), 1.75 (apparent quintet, J = 5.8 Hz, 2H). SFC separation was performed by Chiral Technology OJ-H column, eluting with 25% methanol in CO_2 to afford Enantiomer 1 (3.55 minutes – I-16-A) and Enantiomer 2 (4.67 minutes – I-16-B).

Intermediate 17

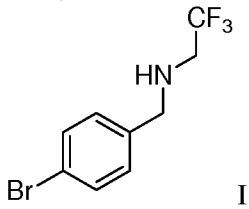
5-bromo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-isoindol-1-one



5-Bromo-2,3-dihydro-1*H*-isoindol-1-one (100 mg, 0.47 mmol) was dissolved in DMF (4.7 mL) and stirred at 0 °C. NaH (38 mg, 0.94 mmol, 60 wt.% dispersion in oil) was carefully added in two portions, and the resulting mixture was allowed to stir at 0 °C for 15 minutes before 2,2,2-trifluoroethyl trifluoromethanesulfonate (110 mg, 0.47 mmol) was added. The mixture was allowed to stir at 0 °C for 30 minutes before saturated aqueous $NaHCO_3$ (10 mL) was carefully added, and the mixture was extracted with EtOAc. The organic layer was washed with water, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified silica chromatography, eluting with 0–20% EtOAc in hexanes. Desired fractions were concentrated *in vacuo* to afford the title compound, I-17. LRMS (ESI) calc'd for $C_{10}H_8BrF_3NO$ $[M+H]^+$: 294, found: 294.

Intermediate 18

N-(4-bromobenzyl)-2,2,2-trifluoroethanamine



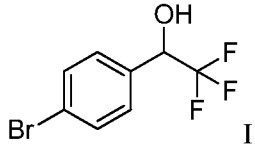
I-18

To a solution of 4-bromobenzylbromide (0.50 g, 2.0 mmol) in CH_3CN (8.0 mL) was added 2,2,2-trifluoroethanamine (0.60 g, 6.1 mmol) and Cs_2CO_3 (0.97 g, 3.0 mmol). The mixture was stirred at 40 °C for 8 hours, then partitioned between water and EtOAc. The organic phase was

washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica chromatography, eluting with 9% EtOAc in hexanes to afford I-18. LRMS (ESI) calc'd for $C_9H_{10}NBrF_3$ $[M+H]^+$: 268, found 268. ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 3.83 (s, 2H), 3.18–3.10 (q, J = 9.6 Hz, 2H).

Intermediate 19

(*R* and *S*)-1-(4-bromophenyl)-2,2,2-trifluoroethanol

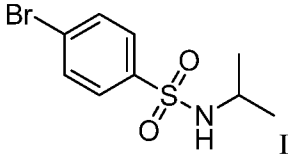


I-19

To a solution of 1-(4-bromophenyl)-2,2,2-trifluoroethanone (1.0 g, 3.95 mmol) in THF (10 mL) was added sodium borohydride (164 mg, 4.35 mmol). The mixture was stirred at room temperature for 2 hours, then quenched with water and concentrated *in vacuo*. The resulting residue was extracted with CH_2Cl_2 (× 2), and the combined organic layers were washed with brine (× 2), dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 1-(4-bromophenyl)-2,2,2-trifluoroethanol as a colorless liquid. ^1H NMR (600 MHz, DMSO-*d6*): δ 7.58 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 6.90 (d, J = 5.6 Hz, 1H), 5.16 (m, 1H). Separation of the enantiomers was achieved by SFC using a Chiral Technologies OJ-H, eluting with 5% isopropanol modifier in CO_2. Retention times = 4.1 (enantiomer A – Intermediate 19A) & 5.1 (enantiomer B – Intermediate 19B) minutes.

Intermediate 20-1

4-bromo-*N*-isopropylbenzenesulfonamide

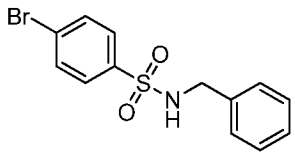
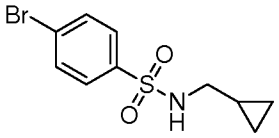
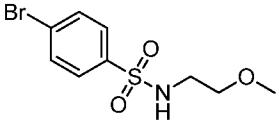
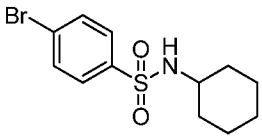
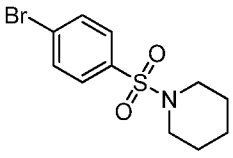


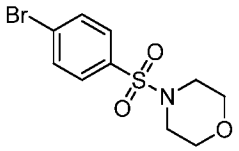
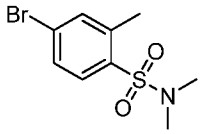
I-20-1

To a solution of propan-2-amine (0.16 g, 2.6 mmol) and DIPEA (0.78 g, 6.0 mmol) in CH_2Cl_2 (7 mL) was added a solution of compound 4-bromophenylsulfonyl chloride (0.51 g, 2.0 mmol) in CH_2Cl_2 (14 mL). The mixture was stirred at room temperature overnight, then poured into water and extracted with CH_2Cl_2 (× 3). The organic layer was concentrated *in vacuo* and the residue was purified by silica chromatography, eluting with 5% EtOAc in hexanes. Concentration of the desired fractions afforded the title compound I-20-1. ^1H NMR (400 MHz, $CDCl_3$): δ δ 7.75–7.72 (m, 2H), 7.65–7.62 (m, 2H), 4.43 (d, J = 7.5 Hz, 1H), 3.49–3.44 (m, 1H), 1.08 (d, J = 6.4 Hz, 6H).

Following the analogous procedure outlined for I-20-1 above, the following aryl bromides in Table 4 were prepared:

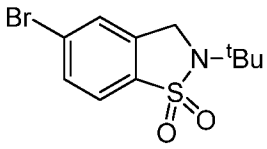
Table 4

Intermediate #	Structure	Compound Name	NMR
I-20-2		*N*-benzyl-4-bromobenzenesulfonamide	^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 5.8 Hz, 2H), 7.70 (d, *J* = 5.8 Hz, 2H), 7.46–7.44 (m, 3H), 7.27–7.17 (m, 2H), 4.78–4.75 (m, 1H), 4.14 (d, *J* = 6 Hz, 2H).
I-20-3		4-bromo-*N*-(cyclopropylmethyl)-benzenesulfonamide	^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 5.6 Hz, 2H), 7.63 (d, *J* = 5.6 Hz, 2H), 4.48–4.45 (m, 1H), 2.77–2.73 (m, 2H),0.81–0.76 (m, 1H) 0.47–0.38 (m, 2H), 0.27–0.25 (m, 2H).
I-20-4		4-bromo-*N*-(2-methoxyethyl)benzene-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 5.8 Hz, 2H), 7.70 (d, *J* = 5.8 Hz, 2H), 4.48–4.45 (m, 1H), 3.49–3.84 (m,2H), 3.30 (s, 3H), 3.13–3.09 (m, 2 H).
I-20-5		4-bromo-*N*-cyclohexylbenzene-sulfonamide	^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75–7.73 (m, 2H), 7.64–7.61(m, 2H), 4.70 (d, *J* = 7.6 Hz, 1H), 3.17–3.09 (m, 1H), 1.75–1.72 (m, 2H), 1.64–1.59 (m, 2H), 1.52–1.48 (m, 1H), 1.24–1.14 (m, 2H).
I-20-6		1-((4-bromophenyl)sulfonyl) piperidine	^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66–7.63 (m, 2H), 7.61–7.58 (m, 2 H), 2.98–2.95 (m, 4H), 1.66–1.57 (m, 4H), 1.44–1.40 (m, 2H).

I-20-7		4-((4-bromophenyl)sulfonyl) morpholine	^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.67 (m, 2H), 7.62–7.59 (m, 2H), 3.74–3.72 (m, 4H), 2.30–2.97 (m, 4H).
I-20-8		4-bromo-*N*,*N*,2-trimethylbenzene-sulfonamide	^{1}H NMR (600 MHz, $CDCl_3$): δ 7.75 (d, J = 8.1 Hz, 1H), 7.50 (m, 1H), 7.47 (dm, J = 8.3 Hz, 1H), 2.80 (s, 6H), 2.61 (s, 3H).

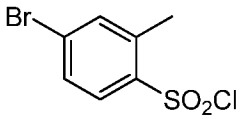
Intermediate 21-1

5-bromo-2-(*tert*-butyl)-2,3-dihydrobenzo[*d*]isothiazole-1,1-dioxide



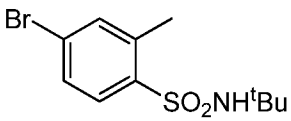
I-21-1

Step 1: <u>4-bromo-2-methylbenzene-1-sulfonyl chloride</u>



Chlorosulfonic acid (63 g, 0.54 mol) was added slowly to a cold solution (0 °C) of 1-bromo-3-methylbenzene (10.0 g, 58 mmol) in $CHCl_3$ (100 mL). The reaction was allowed to proceed with stirring for 2 hours at 0°C, then the reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was then washed with brine, dried over $NaSO_4$, filtered and concentrated *in vacuo* to afford 4-bromo-2-methylbenzene-1-sulfonyl chloride as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 8.4 Hz, 1H), 7.59–7.53 (m, 2H), 2.75 (s, 3H).

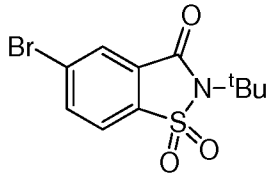
Step 2: <u>4-bromo-*N*-(*tert*-butyl)-2-methylbenzenesulfonamide</u>



To a solution of 4-bromo-2-methylbenzene-1-sulfonyl chloride (2.0 g, 7.4 mmol) in CH_2Cl_2 (15 mL) was added a solution of 2-methylpropan-2-amine (0.65 g, 8.9 mmol) and triethylamine (0.90 g, 8.9 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours and then at room temperature for 16 hours. The mixture was washed with 0.1 M

HCl, saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 4-bromo-*N*-(*tert*-butyl)-2-methylbenzenesulfonamide as a white solid. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.78 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 1.6 Hz, 1H), 7.59–7.56 (m, 2H), 2.57 (s, 3H), 1.09(s, 9H).

Step 3: 5-bromo-2-(*tert*-butyl)benzo[*d*]isothiazol-3(2*H*)-one-1,1-dioxide



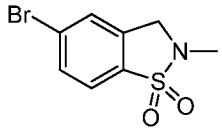
A mixture of H_5IO_6 (5.9 g, 26 mmol) in acetonitrile (50 mL) was stirred at room temperature for 1 hour, then CrO_3 (33 mg, 0.33 mmol) was added followed by acetic anhydride (2.67 g, 26 mmol). The resulting orange solution was cooled to 0 °C, 4-bromo-*N*-(*tert*-butyl)-2-methyl benzenesulfonamide (1.0 g, 3.3 mmol) was added. After stirring at 0 °C for 15 minutes, the reaction was allowed to warm to room temperature and was stirred for 16 hours. The solvent was removed *in vacuo* and the residue was extracted with EtOAc (× 3). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica chromatography, eluting with 5% EtOAc in hexanes and the desired fractions were concentrated *in vacuo* to afford 5-bromo-2-(*tert*-butyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide as a white solid. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.82–8.14 (m, 3H), 1.66 (s, 9H).

Step 4: 5-bromo-2-(*tert*-butyl)-2,3-dihydrobenzo[*d*]isothiazole-1,1-dioxide

To a solution of 5-bromo-2-(*tert*-butyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (0.20 g, 0.63 mmol) in THF (4 mL) was added $BH_3{\cdot}Me_2S$ (240 mg, 3.16 mmol). The reaction mixture was refluxed for 16 hours. After being cooled to room temperature, the reaction was quenched with 2 M HCl, and extracted with EtOAc (× 2), the combined extracts were washed with brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by preparative TLC to afford compound I-21-1. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.83–7.56 (m, 3H), 4.55 (s, 2H), 1.46 (s, 9H).

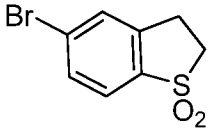
Following an analogous method to that outlined for I-21-1 above, the following intermediates in Table 5 were prepared:

Table 5

Intermediate #	Structure	Compound Name	NMR
I-21-2		5-bromo-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide	^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63–7.60 (m, 2H), 7.5 (s, 1H), 4.25 (s, 2H), 2.89 (s, 3H).

Intermediate 22

5-bromo-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide

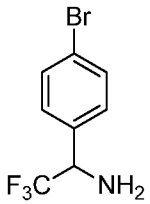


I-22

To a solution of 5-bromo-benzo[*b*]thiophene 1,1-dioxide (1.0 g, 4.1 mmol) in ethanol (13.6 mL) at 0 °C, was added sodium borohydride (193 mg, 5.10 mmol). The resulting reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was then cooled to 0 °C and quenched with 1N HCl. The mixture was extracted with ethyl acetate (× 4) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude oil was purified by silica chromatography, eluting with 20% EtOAc in hexanes to give I-22. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62–7.53 (m, 2H), 7.51 (s, 1H), 3.55–3.45 (m, 2H), 3.39–3.29 (m, 2H).

Intermediate 23

1-(4-bromophenyl)-2,2,2-trifluoroethanamine



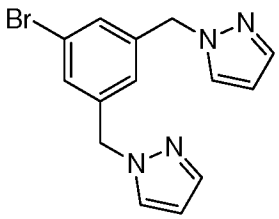
I-23

To a solution of 1-(4-bromophenyl)-2,2,2-trifluoroethanone (1.00 g, 3.95 mmol) in toluene (14 mL) at room temperature, was added (dropwise) a solution of lithium bis(trimethylsilyl)amide (4.35 mL, 4.35 mmol, 1M in THF). The reaction was stirred at room temperature for 15 minutes and then BH_3·THF (7.90 mL, 7.90 mmol, 1M in THF) was added. The reaction was stirred at room temperature for 20 minutes, then quenched at 0 °C by slow addition of 2M aqueous NaOH (5.93 mL, 11.9 mmol). The mixture was stirred at room

temperature for 90 minutes, then the organic layer was separated and washed with 1N aqueous NaOH solution, dried over Na_2SO_4, filtered and concentrated *in vacuo*. SFC separation of the enantiomers on the crude reaction mixture was achieved using a ChiralPak AZ-H, with 7% methanol modifier in CO_2: retention times = 2.37 (I-23A) & 2.89 (I-23B) minutes. LRMS (ESI) calc'd for $C_8H_8NBrF_3$ $[M+H]^+$: 254, found 254. ^1H NMR (600 MHz, $CDCl_3$): δ 7.53 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 4.38 (q, J = 7.5 Hz, 1H), 1.78 (br s, 2H).

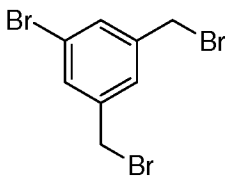
Intermediate 24-1

1,1'-((5-bromo-1,3-phenylene)bis(methylene))bis(1*H*-pyrazole)



I-24-1

Step 1: 1-bromo-3,5-bis(bromomethyl)benzene



To 1-bromo-3,5-dimethylbenzene (5.00 g, 27.0 mmol), 1-bromopyrrolidine-2,5-dione (7.20 g, 40.5 mmol), (*Z*)-2,2'-(diazene-1,2-diyl)bis(2-methylpropanenitrile) (0.045 g, 0.27 mmol) under nitrogen, was added acetonitrile (80 mL). The resulting solution was stirred for 1 hour at 80 °C and then diluted with saturated aqueous ammonium chloride solution and extracted with dichloromethane (× 3). The combined organic layers were concentrated *in vacuo* and the residue was purified by silica chromatography, eluting with hexanes to afford, after concentration of the desired fractions, 1-bromo-3,5-bis(bromomethyl)benzene as an off-white solid.

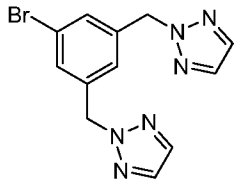
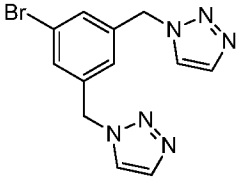
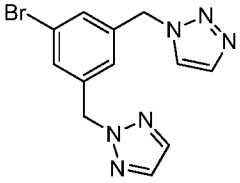
Step 2: 1,1'-((5-bromo-1,3-phenylene)bis(methylene))bis(1*H*-pyrazole)

A solution of 1*H*-pyrazole (1.80 g, 26.4 mmol) in acetonitrile (120 mL) and potassium carbonate (3.60 g, 26.1 mmol) was stirred under nitrogen at 25 °C for hour, then 1-bromo-3,5-bis(bromomethyl)benzene (3.00 g, 8.75 mmol) was added to the mixture and the solution was stirred for 16 additional hours. The reaction was then quenched by addition of saturated aqueous ammonium chloride solution, extracted with ethyl acetate (× 3), and the organic layers were combined, dried over sodium sulfate, filtered and concentrated *in vacuo*.

The crude product was purified by silica chromatography, eluting with 50% EtOAc in hexanes. Concentration of the desired fractions affoded compound I-24-1 as a colorless solid. LRMS (ESI) calc'd for $C_{14}H_{14}N_4Br$ $[M+H]^+$: 317, found 317.

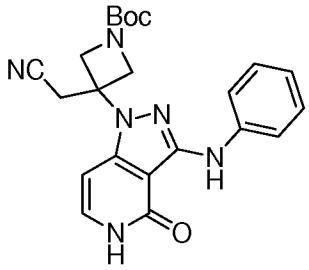
Following the general procedure outlined above for I-24-1, the intermediates shown in Table 6 were prepared:

Table 6:

Intermediate #	Structure	Compound Name	LCMS
I-24-2		2,2'-((5-bromo-1,3-phenylene)bis(methylene))bis(2*H*-1,2,3-triazole)	LRMS (ESI) calc'd for $C_{12}H_{12}N_6Br$ $[M+H]^+$: 319, found 319.
I-24-3		1,1'-((5-bromo-1,3-phenylene)bis(methylene))bis(1*H*-1,2,3-triazole)	LRMS (ESI) calc'd for $C_{12}H_{12}N_6Br$ $[M+H]^+$: 319, found 319.
I-24-4		1-(3-((2*H*-1,2,3-triazol-2-yl)methyl)-5-bromobenzyl)-1*H*-1,2,3-triazole	LRMS (ESI) calc'd for $C_{12}H_{12}N_6Br$ $[M+H]^+$: 319, found 319.

Example 1-1

tert-butyl 3-(cyanomethyl)-3-(4-oxo-3-(phenylamino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)azetidine-1-carboxylate

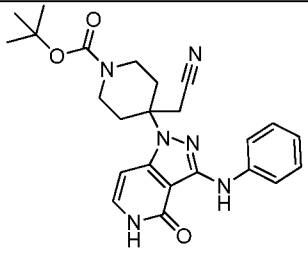


1-1

3-(Phenylamino)-1*H*-pyrazolo[4,3-*c*]pyridin-4(5*H*)-one (11.3 mg, 0.0499 mmol) and *tert*-butyl 3-(cyanomethylene)azetidine-1-carboxylate (17.0 mg, 0.088 mmol) were dissolved in DMF (1.0 mL). DBU (14 μL, 0.093 mmol) was added and the reaction mixture was stirred overnight at room temperature. After 18 hours the reaction mixture was diluted in EtOAc and washed with saturated aqueous sodium hydrogen carbonate and brine. The combined aqueous layers were back extracted with 3:1 chloroform/isopropanol (× 1) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica chromatography, eluting with a 10–100% EtOAc/isohexane, followed by a 0–5% MeOH/EtOAc gradient to afford compound 1-1. LRMS (ESI) calc'd for $C_{22}H_{25}N_6O_3$ $[M+H]^+$: 421, found 421. ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.28 (s, 1H), 8.06 (s, 1H), 7.62–7.56 (m, 2H), 7.28–7.19 (m, 3H), 6.86 (dd, *J* = 7.2, 6.6 Hz, 1H), 6.36 (dd, *J* = 7.2, 1.8 Hz, 1H), 4.46 (d, *J* = 8.4 Hz, 2H), 4.25 (d, *J* = 6.6 Hz, 2H), 3.41 (s, 2 H), 1.36 (s, 9H).

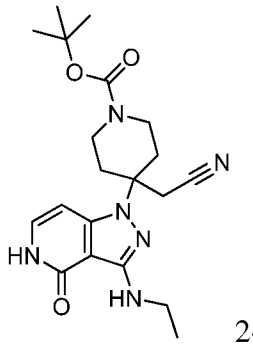
The following examples outlined in Table 7 were prepared by analogy using the general procedure outlined above for compound 1-1, using 1.2 equivalents DBU, 1.5 equivalents Michael acceptor in DMF (0.15 M) at 50°C.

Table 7

Example	Structure	Compound Name	LCMS
1-2		*tert*-butyl 4-(cyanomethyl)-4-(4-oxo-3-(phenylamino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{24}H_{29}N_6O_3$ $[M+H]^+$: 449, found 449.

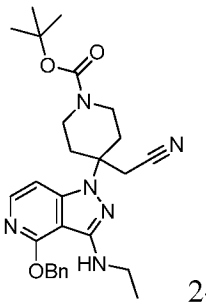
Example 2-1

tert-butyl 4-(cyanomethyl)-4-[3-(ethylamino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate



2-1

Step 1: *tert*-butyl 4-(4-(benzyloxy)-3-(ethylamino)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate



2-1a

To a solution of *tert*-butyl 4-[3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]-4-(cyanomethyl)piperidine-1-carboxylate (20 mg, 0.043 mmol) in dichloroethane (0.30 mL) was added a solution of acetaldehyde (3.0 μL, 0.054 mmol) and acetic acid (2.5 μL, 0.043 mmol) in dichloroethane (0.24 mL). This mixture was stirred at room temperature for 10 minutes before sodium triacetoxyborohydride (16 mg, 0.076 mmol) was added. The reaction was stirred at room temperature for 5.5 hours, then diluted with EtOAc and washed with 1N NaOH and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica chromatography, eluting with 0–100% EtOAc/hexanes to afford compound 2-1a. LRMS (ESI) calc'd for $C_{27}H_{35}N_6O_3$ $[M+H]^+$: 491, found 491.

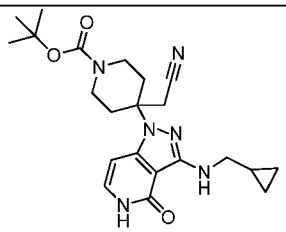
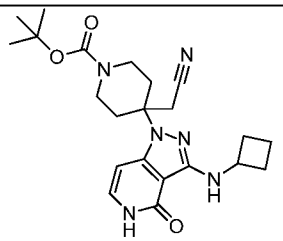
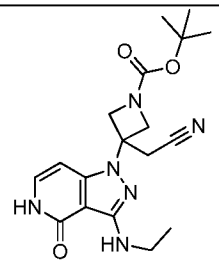
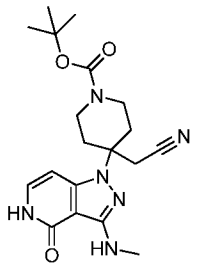
Step 2: *tert*-butyl 4-(cyanomethyl)-4-[3-(ethylamino)-4-oxo-4,5-dihydro-1*H*-pyrazolo-[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate

tert-Butyl 4-(4-(benzyloxy)-3-(ethylamino)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate (2-1a) (9.0 mg, 0.018 mmol) was dissolved in EtOAc (2.0 mL) and EtOH (0.20 mL). Pd/C (10 mg, 0.094 mmol) was added and the reaction was stirred under 1 atmosphere of hydrogen for 2 hours. The reaction was then filtered through Celite and washed with DCM and the filtrate was concentrated *in vacuo*. The crude reaction mixture was purified by silica chromatrography, eluting with 100% EtOAc. Concentration of the desired fractions afforded compound 2-1. LRMS (ESI) calc'd for $C_{20}H_{29}N_6O_3$ $[M+H]^+$: 401, found 401. ^{1}H NMR (600 MHz, DMSO-*d6*) δ 10.93 (d, *J* = 5.0 Hz, 1H), 7.01 (t, *J* = 6.6 Hz, 1H),

6.49 (d, *J* = 7.5 Hz, 1H), 5.42 (t, *J* = 5.8 Hz, 1H), 3.68 (d, *J* = 13.8 Hz, 2H), 3.18 (dt, *J* = 13.4 Hz, 6.8, 2H), 3.10 (s, 2H), 2.98 (br s, 2H), 2.57 (d, *J* = 13.9 Hz, 2H), 1.85 (t, *J* = 10.2 Hz, 2H), 1.35 (s, 9H), 1.12 (t, *J* = 7.1 Hz, 3H).

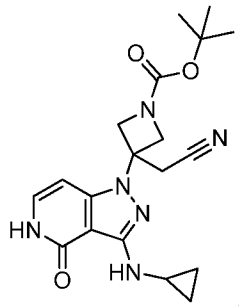
The following Examples shown in Table 8 were prepared in analogy to Example 2-1 above:

Table 8

Example	Structure	Compound Name	LRMS
2-2		*tert*-butyl 4-(cyanomethyl)-4-{3-[(cyclopropylmethyl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{22}H_{31}N_6O_3$ $[M+H]^+$: 427, found 427
2-3		*tert*-butyl 4-(cyanomethyl)-4-[3-(cyclobutylamino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{22}H_{31}N_6O_3$ $[M+H]^+$: 427, found 427
2-4		*tert*-butyl 3-(cyanomethyl)-3-[3-(ethylamino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]azetidine-1-carboxylate	LRMS (ESI) calc'd for $C_{18}H_{25}N_6O_3$ $[M+H]^+$: 373, found 373
2-5		*tert*-butyl 4-(cyanomethyl)-4-[3-(methylamino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{19}H_{27}N_6O_3$ $[M+H]^+$: 387, found 387

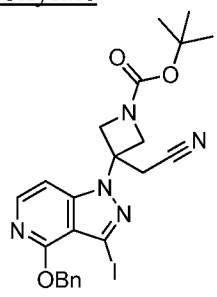
Example 3

tert-butyl 3-(cyanomethyl)-3-[3-(cyclopropylamino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]azetidine-1-carboxylate



3

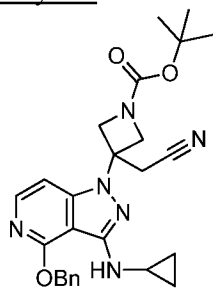
Step 1: *tert*-butyl 3-[4-(benzyloxy)-3-iodo-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]-3-(cyanomethyl)azetidine-1-carboxylate



3a

To a solution of *tert*-butyl 3-[3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]-3-(cyanomethyl)azetidine-1-carboxylate (250 mg, 0.575 mmol) in dichloroethane (10 mL) was added I_2 (365 mg, 1.44 mmol). The mixture was stirred for 10 minutes under nitrogen and was then cooled to 0 °C and *tert*-butyl nitrite (0.137 mL, 1.15 mmol) was added dropwise. The reaction was stirred at 0 °C for 10 minutes, then warmed to room temperature and stirred for 2 additional hours. The reaction was diluted with EtOAc (100 mL) and washed with aqueous $NaHSO_3$, brine, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica chromatography, eluting with 0–75% EtOAc in hexanes to afford compound 3a. LRMS (ESI) calc'd for $C_{23}H_{25}IN_5O_3$ $[M+H]^+$: 546, found 546. ^1H NMR (600 MHz, $CDCl_3$): δ 7.96 (d, J = 6.0 Hz, 1H), 7.58 (d, J = 7.8 Hz, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 6.87 (d, J = 6.6 Hz, 1H), 5.59 (s, 2H), 4.66 (d, J = 9.6 Hz, 2H), 4.33 (d, J = 9.0 Hz, 2H), 3.16 (s, 2H), 1.44 (s, 9H).

Step 2: *tert*-butyl 3-[4-(benzyloxy)-3-(cyclopropylamino)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]-3-(cyanomethyl)azetidine-1-carboxylate



3b

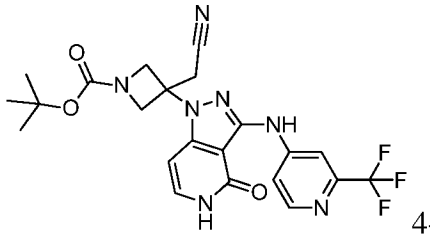
A vial equipped with a stir bar was charged with CuI (4.4 mg, 0.023 mmol), potassium phosphate tribasic (24.3 mg, 0.115 mmol), L-proline (5.3 mg, 0.046 mmol), *tert*-butyl 3-[4-(benzyloxy)-3-iodo-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]-3-(cyanomethyl)azetidine-1-carboxylate (25 mg, 0.046 mmol) and DMSO (460 μL). The mixture was sparged with nitrogen for 2 minutes and then cyclopropylamine (22 μL, 0.32 mmol) was added. The mixture was sparged with nitrogen for an additional 2 minutes and then the vial was sealed and heated to 80 °C for 2 hours. The reaction was cooled to room temperature, diluted with EtOAc, and the organic layers were washed with water, brine, and dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by silica chromatography, eluting with 0–100% EtOAc in hexanes followed by further purification by preparatory thin layer chromatography (PTLC) with 2% MeOH/CH_2Cl_2 (3 elutions) afforded compound 3b. LRMS (ESI) calc'd for $C_{26}H_{31}N_6O_3$ $[M+H]^+$: 475, found 475. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.82 (d, *J* = 6.0 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 1H), 6.64 (d, *J* = 6.0 Hz, 1H), 5.51 (s, 2H), 5.06 (s, 1H), 4.65 (d, *J* = 9.6 Hz, 2H), 4.26 (d, *J* = 9.0 Hz, 2H), 3.08 (s, 2H), 2.63 (m, 1H), 1.45 (s, 9H), 0.71 (m, 2H), 0.51 (m, 2H).

Step 3: <u>*tert*-butyl 3-(cyanomethyl)-3-[3-(cyclopropylamino)-4-oxo-4,5-dihydro-1*H*-pyrazolo-[4,3-*c*]pyridin-1-yl]azetidine-1-carboxylate</u>

To a solution of *tert*-butyl 3-[4-(benzyloxy)-3-(cyclopropylamino)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]-3-(cyanomethyl)azetidine-1-carboxylate (3.0 mg, 0.0063 mmol) in EtOAc (1 mL) was added 10% Pd/C (5 mg). The reaction was stirred under 1 atmosphere of hydrogen at room temperature for 2 hours. The balloon of hydrogen was removed and the reaction was filtered through Celite (washing with DCM) and the filtrate concentrated *in vacuo*. The residue was purified by preparatory thin layer chromatography (PTLC) with 4% MeOH/CH_2Cl_2 to afford compound 3. LRMS (ESI) calc'd for $C_{19}H_{25}N_6O_3$ $[M+H]^+$: 385, found 385. ^{1}H NMR (600 MHz, DMSO-*d6*): δ 10.98 (d, *J* = 6.0 Hz, 1H), 7.09 (dd, *J* = 7.2, 6.0 Hz, 1H), 6.20 (d, *J* = 7.2 Hz, 1H), 5.67 (d, *J* = 2.4 Hz, 1H), 4.41 (m, 2H), 4.19 (m, 2H), 3.29 (s, 2H), 2.54 (m, 1H), 1.36 (s, 9H), 0.59 (m, 2H), 0.48 (m, 2H).

Example 4-1

tert-butyl 3-(cyanomethyl)-3-(4-oxo-3-((2-(trifluoromethyl)pyridin-4-yl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)azetidine-1-carboxylate

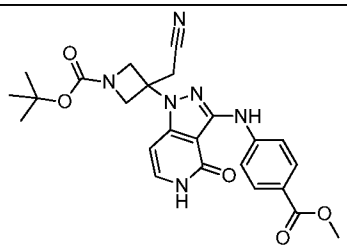
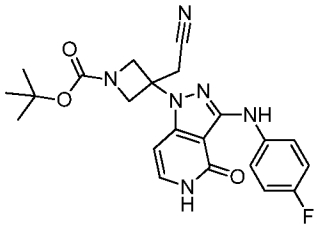


4-1

To a vial was charged with *tert*-butyl 3-(3-amino-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-3-(cyanomethyl)azetidine-1-carboxylate (35 mg, 0.10 mmol), 4-bromo-2-trifluoromethyl pyridine (34.5 mg, 0.152 mmol), $Pd_2(dba)_3$ (4.65 mg, 5.08 μmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (12 mg, 0.020 mmol), and Cs_2CO_3 (66.2 mg, 0.203 mmol). Dioxane (0.68 mL) was added and the mixture was purged with argon for 5 minutes. The vial was then sealed and heated at 90 °C for 3 hours. The mixture was cooled and filtered through Celite with 3:1 $CHCl_3$:IPA and the resulting solution was concentrated *in vacuo*. The residue was taken up in DMSO and purified by mass triggered reverse phase HPLC, eluting with acetonitrile/water containing 0.1% TFA modifier. Fractions containing desired product were diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford compound 4-1. LRMS (ESI) calc'd for $C_{22}H_{23}F_3N_7O_3$ [M+H]+: 490, found 490. ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.36 (s, 1H), 9.20 (s, 1H), 8.42 (d, J = 4.8 Hz, 1H), 8.17 (s, 1H), 7.87 (m, 1H), 7.25 (m, 1H), 6.40 (d, J = 7.2 Hz, 1H), 4.47 (m, 2H), 4.27 (d, J = 8.4 Hz, 2H), 3.45 (s, 2H), 1.36 (s, 9H).

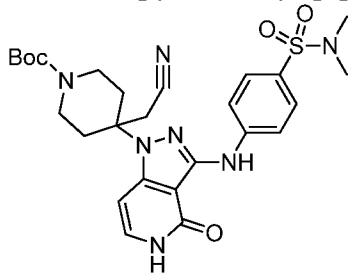
The following Examples in Table 9 were prepared in analogy to Example 4-1:

Table 9

Example	Structure	Compound Name	LCMS
4-2		*tert*-butyl 3-(cyanomethyl)-3-(3((4(methoxycarbonyl) phenyl) amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)azetidine-1-carboxylate	LRMS (ESI) calc'd for $C_{24}H_{27}N_6O_5$ $[M+H]^+$: 479, found 479.
4-3		*tert*-butyl 3-(cyanomethyl)-3-(3-((4-fluorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*] pyridin-1-yl)azetidine-1-carboxylate	LRMS (ESI) calc'd for $C_{22}H_{24}FN_6O_3$ $[M+H]^+$: 439, found 439.

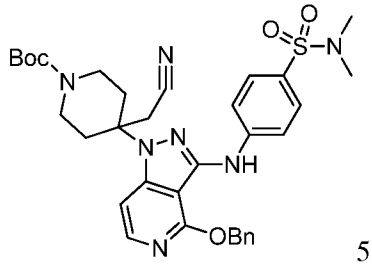
Example 5-1

tert-butyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate



5-1

Step 1: *tert*-butyl 4-(4-(benzyloxy)-3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate



5-1a

To *tert*-butyl 4-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate (3.00 g, 6.49 mmol), 4-bromo-*N*,*N*-dimethylbenzenesulfonamide (3.43 g, 13.0 mmol), Pd_2dba_3 (0.594 g, 0.649 mmol), 2-di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl (0.935 g, 1.95 mmol) and potassium phosphate tribasic (2.75 g, 13.0 mmol) in a degassed sealed microwave vial, was added *t*-amyl alcohol (86 mL) and the reaction was degassed again by evacuation/argon backfill (×3) and heated to 75 °C overnight. The reaction was concentrated and purified by silica chromatography, eluting with 10–80% EtOAc in hexanes. The desired product, 5-1a, was collected and concentrated *in vacuo* to afford the desired product as a light brown solid. LRMS (ESI) calc'd for $C_{33}H_{40}N_7O_5S$ $[M+H]^+$: 646, found 646. ^1H NMR (600 MHz, DMSO-*d6*): δ 8.53 (s, 1 H), 7.85 (d, 1H, J = 6.0 Hz), 7.68 (d, 2H, J = 9.0 Hz), 7.60 (d, 2H, J = 9.0 Hz), 7.46 (d, 2H, J = 7.8 Hz), 7.35 (m, 3H), 7.28 (m, 1H), 5.57 (s, 2H), 3.75 (d, 2H, J = 14.4 Hz), 3.28 (s, 2H), 3.03 (bs, 2H), 2.74 (d, 2H, J = 14.4 Hz), 2.47 (s, 6H), 2.03 (t, 2H, J = 10.8 Hz), 1.37 (s, 9H).

Step 2: *tert*-butyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate

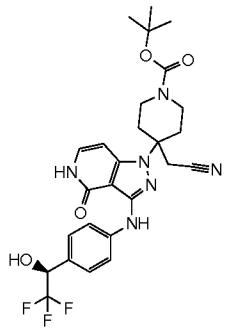
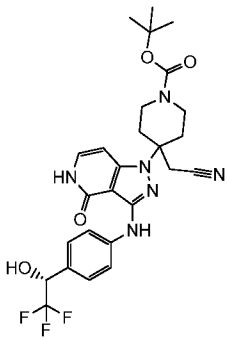
To *tert*-butyl 4-(4-(benzyloxy)-3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate (3.37 g, 5.22 mmol) was added Pd/C (10 wt% Pd loading, 0.27 g) and ethyl acetate (26 mL). The suspension was then

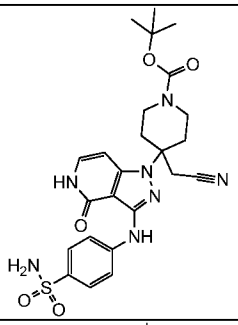
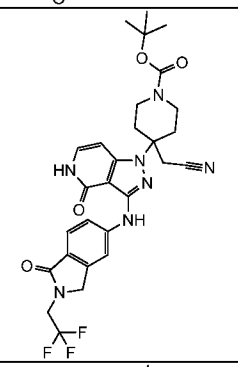
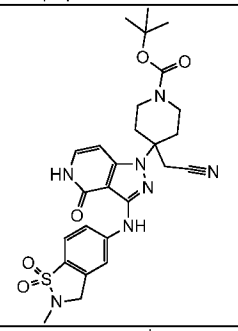
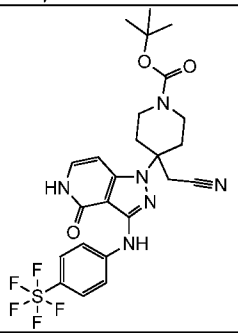
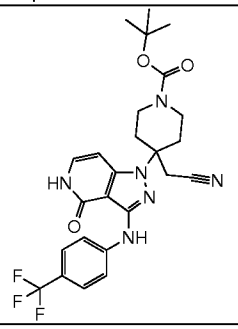
evacuated and backfilled with hydrogen and the reaction was stirred under hydrogen at 1 atmosphere overnight at room temperature. The reaction was filtered through Celite and the filter pad was washed with DCM and the organic solvents were concentrated *in vacuo*. The solid was purified by silica chromatography, eluting with 0–6% methanol in DCM to afford the desired product,

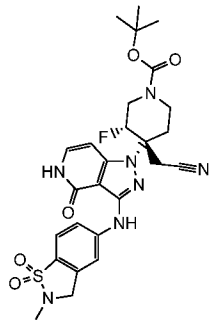
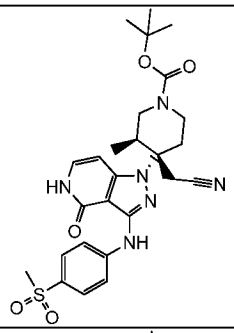
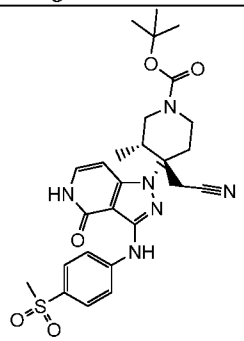
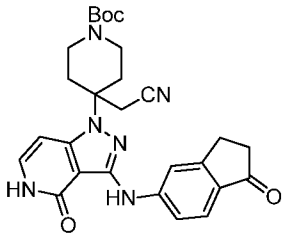
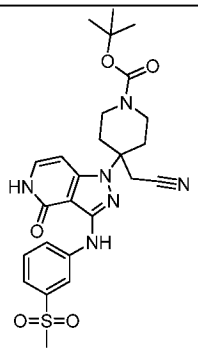
5-1, as a green solid that was triturated from DCM to afford analytically white solid. LRMS (ESI) calc'd for $C_{21}H_{26}N_7O_3S$ $[M\text{-Boc}+H]^+$: 456, found 456. ^1H NMR (600 MHz, DMSO-*d6*): δ 11.33 (s, 1H), 8.68 (s, 1H), 7.82 (d, 2H, J = 9.0 Hz), 7.60 (d, 2H, J = 9.0 Hz), 7.17 (d, 1H, J = 7.8 Hz), 6.67 (d, 1H, J = 7.8 Hz), 3.70 (d, 2H, J = 13.8 Hz), 3.24 (s, 6H), 3.05 (bs, 2H), 2.64 (d, 2H, J = 13.8 Hz), 2.45 (s, 6H), 1.99 (apparent t, 2H, J = 12.0 Hz), 1.35 (s, 9H).

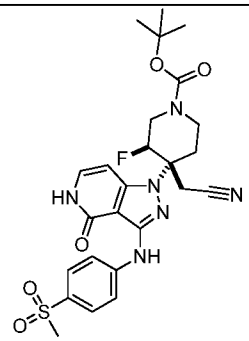
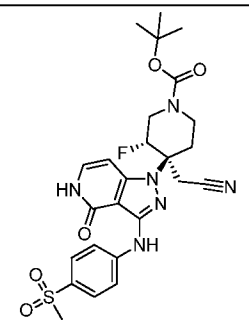
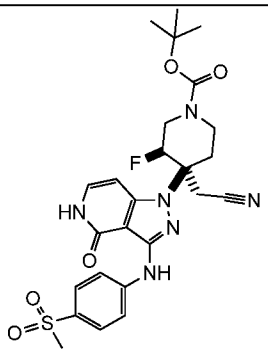
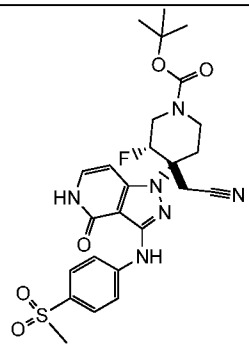
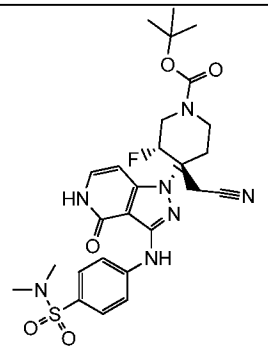
The following examples outlined in Table 10 were prepared by analogy using the general procedure outlined above for Example 5-1.

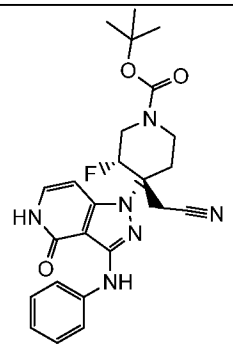
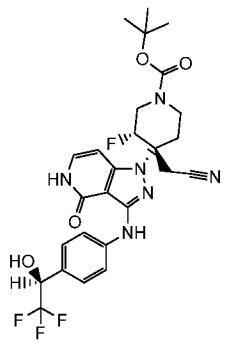
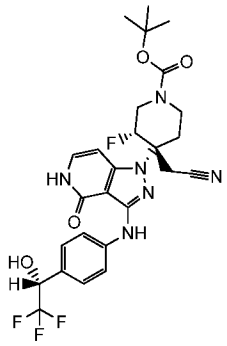
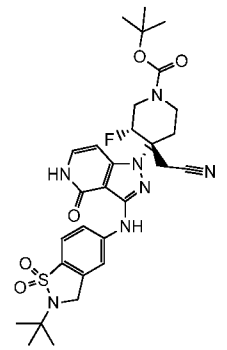
Table 10:

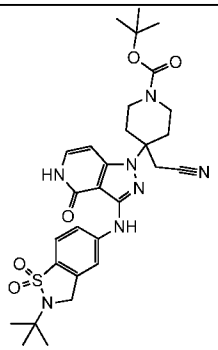
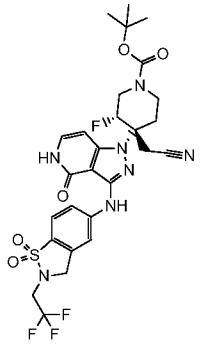
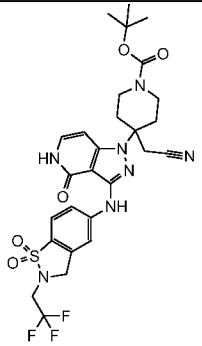
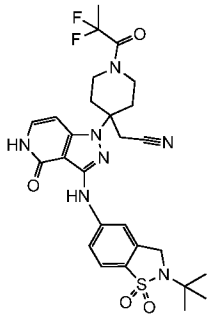
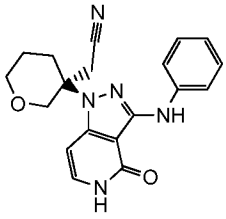
Example	Structure	Compound Name	LRMS
5-2		*tert*-butyl 4-(cyanomethyl)-4-[4-oxo-3-({4-[(1*S* or 1*R*)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{26}H_{30}N_6O_4F_3$ $[M+H]^+$: 547, found 547. SFC retention time (Chiralpak IA, 29% MeOH in CO_2) = 4.4 minutes.
5-3		*tert*-butyl 4-(cyanomethyl)-4-[4-oxo-3-({4-[(1*R* or 1*S*)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{26}H_{30}N_6O_4F_3$ $[M+H]^+$: 547, found 547. SFC retention time (Chiralpak IA, 29% MeOH in CO_2) = 3.7 minutes.

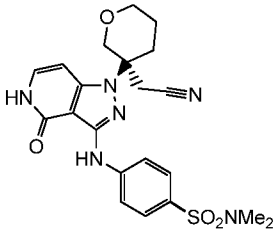
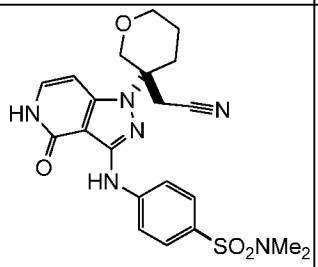
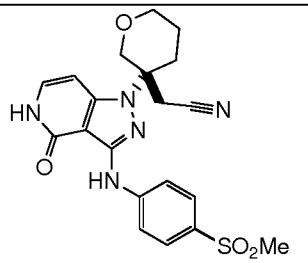
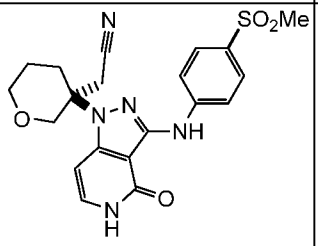
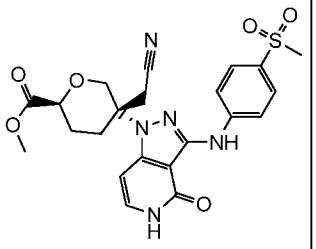
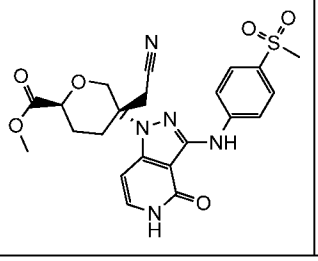
5-4		*tert*-butyl 4-(cyanomethyl)-4-{4-oxo-3-[(4-sulfamoylphenyl)amino]-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{24}H_{30}N_7O_5S$ $[M+H]^+$: 528, found 528.
5-5		*tert*-butyl 4-(cyanomethyl)-4-(4-oxo-3-{[1-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-isoindol-5-yl]amino}-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{28}H_{31}N_7O_4F_3$ $[M+H]^+$: 586, found 586.
5-6		*tert*-butyl 4-(cyanomethyl)-4-{3-[(2-methyl-1,1-dioxido-2,3-dihydro-1,2-benzisothiazol-5-yl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{21}H_{24}N_7O_3S$ $[M-Boc+H]^+$: 454, found 454.
5-7		*tert*-butyl 4-(cyanomethyl)-4-(4-oxo-3-{[4-(pentafluorosulfanyl)phenyl]amino}-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{19}H_{20}N_6OSF_5$ $[M-Boc+H]^+$: 475, found 475.
5-8		*tert*-butyl 4-(cyanomethyl)-4-(4-oxo-3-{[4-(trifluoromethyl)phenyl]amino}-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{25}H_{28}N_6O_3F_3$ $[M+H]^+$: 517, found 517.

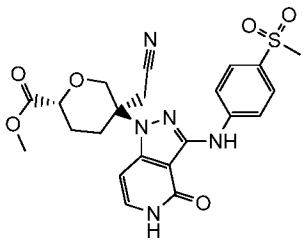
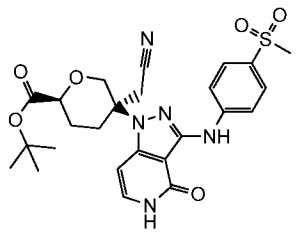
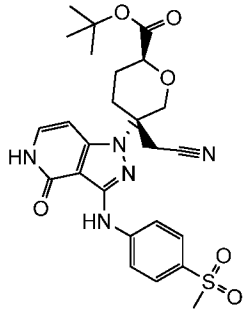
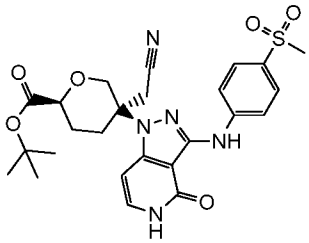
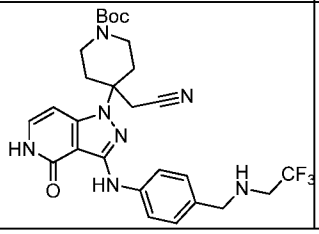
5-9		*tert*-butyl (3*R*,4*R*)-4-(cyanomethyl)-3-fluoro-4-{3-[(2-methyl-1,1-dioxido-2,3-dihydro-1,2-benzisothiazol-5-yl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate (from I-6-2B)	LRMS (ESI) calc'd for $C_{21}H_{23}N_7O_3FS$ $[M\text{-}Boc+H]^+$: 472, found 472.
5-10		*tert*-butyl (3*R*,4*S* and 3*S*,4*R*)-4-(cyanomethyl)-3-methyl-4-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{26}H_{33}N_6O_5S$ $[M+H]^+$: 541, found 541.
5-11		*tert*-butyl (3*S*,4*S* and 3*R*,4*R*)-4-(cyanomethyl)-3-methyl-4-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{26}H_{33}N_6O_5S$ $[M+H]^+$: 541, found 541.
5-12		*tert*-butyl 4-(cyanomethyl)-4-(4-oxo-3-((1-oxo-2,3-dihydro-1*H*-inden-5-yl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{27}H_{31}N_6O_4$ $[M+H]^+$: 503, found 503.
5-13		*tert*-butyl 4-(cyanomethyl)-4-(3-{[3-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{25}H_{31}N_6O_5S$ $[M+H]^+$: 527, found 527.

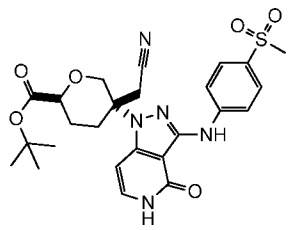
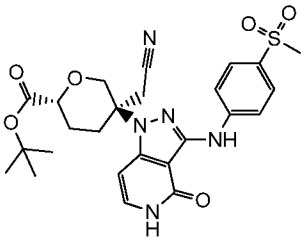
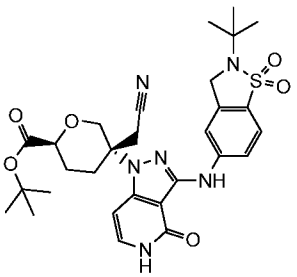
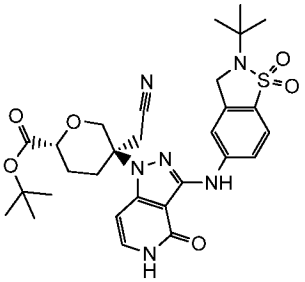
5-14		*tert*-butyl (3*S*,4*R* or 3*R*,4*S*)-4-(cyanomethyl)-3-fluoro-4-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate (from I-6-1A)	LRMS (ESI) calc'd for $C_{25}H_{30}FN_6O_5S$ $[M+H]^+$: 545, found 545.
5-15		*tert*-butyl (3*R*,4*S* or 3*S*,4*R*)-4-(cyanomethyl)-3-fluoro-4-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate (from I-6-1B)	LRMS (ESI) calc'd for $C_{25}H_{30}FN_6O_5S$ $[M+H]^+$: 545, found 545.
5-16		*tert*-butyl (3*S*,4*S*)-4-(cyanomethyl)-3-fluoro-4-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate (from I-6-2A)	LRMS (ESI) calc'd for $C_{25}H_{30}FN_6O_5S$ $[M+H]^+$: 545, found 545.
5-17		*tert*-butyl (3*R*,4*R*)-4-(cyanomethyl)-3-fluoro-4-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate (from I-6-2B)	LRMS (ESI) calc'd for $C_{25}H_{30}FN_6O_5S$ $[M+H]^+$: 545, found 545.
5-18		*tert*-butyl (3*R*,4*R*)-4-(cyanomethyl)-4-(3-{[4-(dimethylsulfamoyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate (from I-6-2B)	LRMS (ESI) calc'd for $C_{26}H_{33}FN_7O_5S$ $[M+H]^+$: 574, found 574.

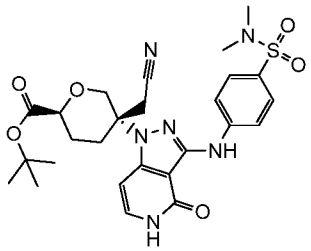
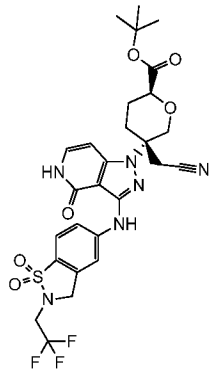
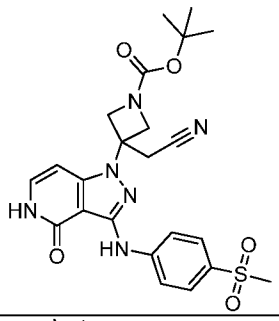
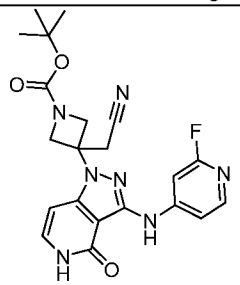
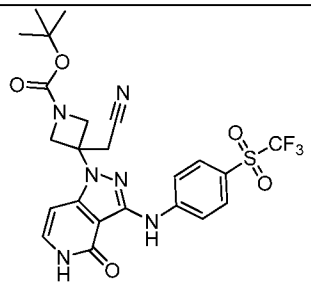
5-19		*tert*-butyl (3*R*,4*R*)-4-(cyanomethyl)-3-fluoro-4-[4-oxo-3-(phenylamino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate (from I-6-2B)	LRMS (ESI) calc'd for $C_{24}H_{28}FN_6O_3$ $[M+H]^+$: 467, found 467.
5-20		*tert*-butyl (3*R*,4*R*)-4-(cyanomethyl)-3-fluoro-4-[4-oxo-3-({4-[(1*S* or 1*R*)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate (from I-6-2B & I-19B)	LRMS (ESI) calc'd for $C_{26}H_{29}F_4N_6O_4$ $[M+H]^+$: 565, found 565.
5-21		*tert*-butyl (3*R*,4*R*)-4-(cyanomethyl)-3-fluoro-4-[4-oxo-3-({4-[(1*R* or 1*S*)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate (from I-6-2B & I-19A)	LRMS (ESI) calc'd for $C_{26}H_{29}F_4N_6O_4$ $[M+H]^+$: 565, found 565.
5-22		*tert*-butyl (3*R*,4*R*)-4-{3-[(2-*tert*-butyl-1,1-dioxido-2,3-dihydro-1,2-benzisothiazol-5-yl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}-4-(cyanomethyl)-3-fluoropiperidine-1-carboxylate (from I-6-2B)	LRMS (ESI) calc'd for $C_{29}H_{37}FN_7O_5S$ $[M+H]^+$: 614, found 614.

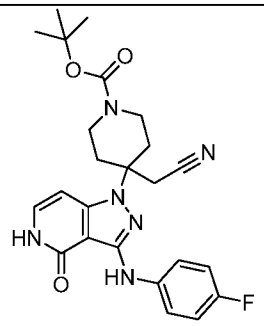
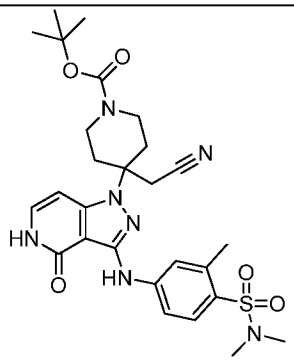
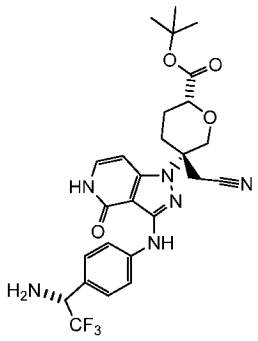
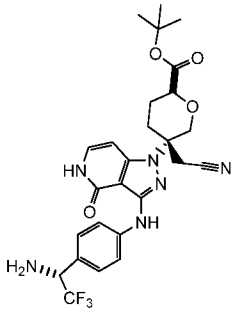
5-23		*tert*-butyl 4-{3-[(2-*tert*-butyl-1,1-dioxido-2,3-dihydro-1,2-benzisothiazol-5-yl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}-4-(cyanomethyl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{29}H_{38}N_7O_5S$ $[M+H]^+$: 596, found 596.
5-24		*tert*-butyl (3*R*,4*R*)-4-(cyanomethyl)-4-(3-{[1,1-dioxido-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1,2-benzisothiazol-5-yl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate (from I-6-2B)	LRMS (ESI) calc'd for $C_{27}H_{30}F_4N_7O_5S$ $[M+H]^+$: 640, found 640.
5-25		*tert*-butyl 4-(cyanomethyl)-4-(3-((1,1-dioxido-2-(2,2,2-trifluoroethyl)-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{27}H_{31}F_3N_7O_5S$ $[M+H]^+$: 622, found 622.
5-26		2-(4-(3-((2-(*tert*-butyl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1-(2,2-difluoropropanoyl)piperidin-4-yl)acetonitrile	LRMS (ESI) calc'd for $C_{27}H_{32}F_2N_7O_4S$ $[M+H]^+$: 588, found 588.
5-27		(*S*)-2-(3-(4-oxo-3-(phenylamino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-3-yl)acetonitrile (from I-16B)	LRMS (ESI) calc'd for $C_{19}H_{20}N_5O_2$ $[M+H]^+$: 350, found 350.

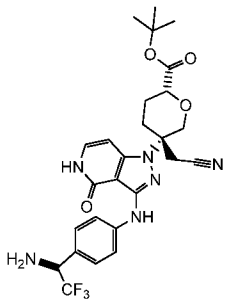
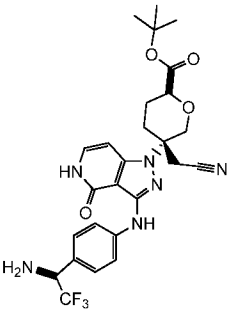
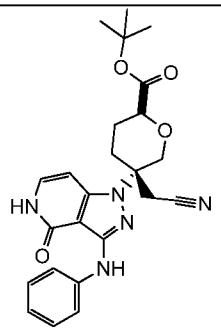
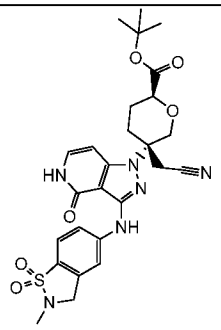
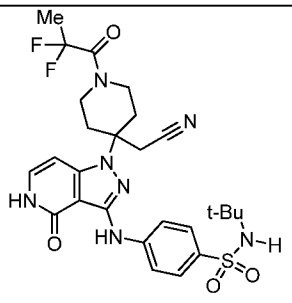
5-28		(*S*)-4-((1-(3-(cyanomethyl)tetrahydro-2*H*-pyran-3-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide (from I-16B)	LRMS (ESI) calc'd for $C_{21}H_{25}N_6O_4S$ $[M+H]^+$: 457, found 457.
5-29		(*R*)-4-((1-(3-(cyanomethyl)tetrahydro-2*H*-pyran-3-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide (from I-16A)	LRMS (ESI) calc'd for $C_{21}H_{25}N_6O_4S$ $[M+H]^+$: 457, found 457.
5-30		(*R*)-2-(3-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-3-yl)acetonitrile (from I-16A)	LRMS (ESI) calc'd for $C_{20}H_{22}N_5O_4S$ $[M+H]^+$: 428, found 428.
5-31		(*S*)-2-(3-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-3-yl)acetonitrile (from I-16B)	LRMS (ESI) calc'd for $C_{20}H_{22}N_5O_4S$ $[M+H]^+$: 428, found 428.
5-32		(2*S*,5*S* *and* 2*R*,5*R*)-methyl 5-(cyanomethyl)-5-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate (racemic mixture)	LRMS (ESI) calc'd for $C_{22}H_{24}N_5O_6S$ $[M+H]^+$: 486, found 486.
5-33		(2*S*,5*S* *or* 2*R*,5*R*)-methyl 5-(cyanomethyl)-5-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-	LRMS (ESI) calc'd for $C_{22}H_{24}N_5O_6S$ $[M+H]^+$: 486, found 486. SFC retention time (AD-H column,

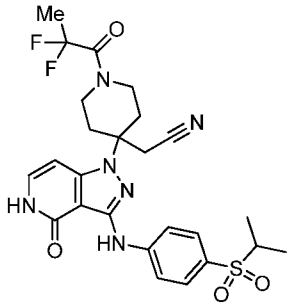
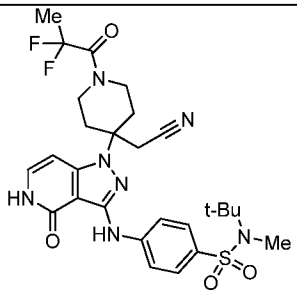
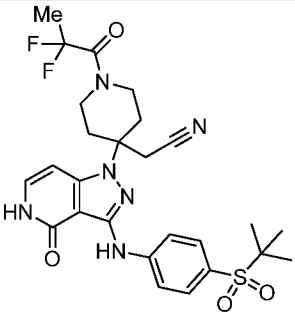
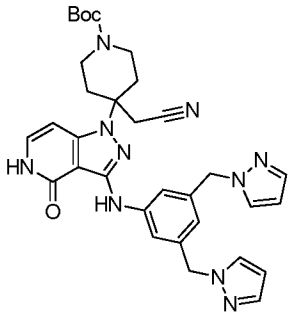
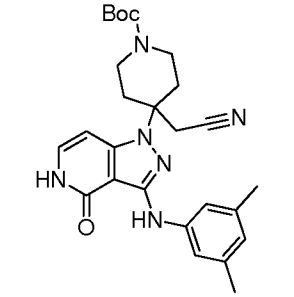
		carboxylate	35% MeOH in CO_2) = 5.9 minutes.
5-34		(2*S*,5*S or* 2*R*,5*R*)-methyl 5-(cyanomethyl)-5-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate	LRMS (ESI) calc'd for $C_{22}H_{24}N_5O_6S$ $[M+H]^+$: 486, found 486. SFC retention time (AD-H column, 35% MeOH in CO_2) = 7.5 minutes.
5-35		(2*R*,5*S and 2S,5R*)-*tert*-butyl 5-(cyanomethyl)-5-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate (from racemic I-13-2)	LRMS (ESI) calc'd for $C_{25}H_{30}N_5O_6S$ $[M+H]^+$: 528, found 528.
5-36		(2*S*,5*S and 2R,5R*)-*tert*-butyl 5-(cyanomethyl)-5-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate (from racemic I-13-1)	LRMS (ESI) calc'd for $C_{25}H_{30}N_5O_6S$ $[M+H]^+$: 528, found 528. .
5-37		(2*R*,5*S or 2S,5R*)-*tert*-butyl 5-(cyanomethyl)-5-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate (from Example 5-35)	LRMS (ESI) calc'd for $C_{25}H_{30}N_5O_6S$ $[M+H]^+$: 528, found 528. SFC retention time (AD-H column, 25% MeOH in CO_2) = 3.8 minutes.
5-38		*tert*-butyl 4-(cyanomethyl)-4-(4-oxo-3-((4-(((2,2,2-trifluoroethyl)amino)methyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-	LRMS (ESI) calc'd for $C_{25}H_{29}N_6O_3$ [M-$NHCH_2CF_3$]$^+$: 461, found 461.

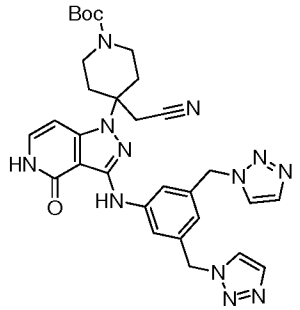
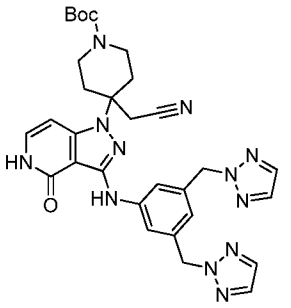
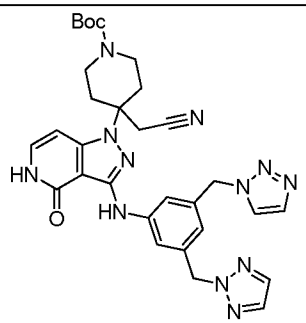
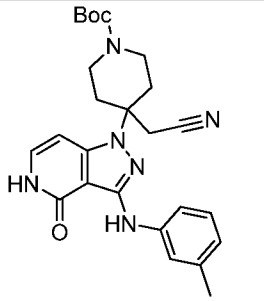
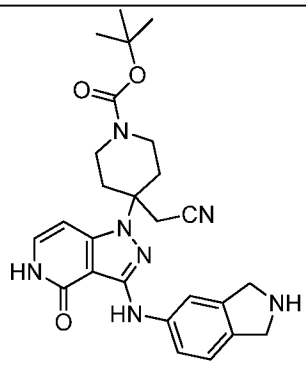
		1-yl)piperidine-1-carboxylate	
5-39		(2*S*,5*S*)-*tert*-butyl 5-(cyanomethyl)-5-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate (from Example 5-36)	LRMS (ESI) calc'd for $C_{25}H_{30}N_5O_6S$ $[M+H]^+$: 528, found 528. LC retention time (IB column, 40% MeOH /EtOH = 3:2, 60% heptanes) = 8.1 minutes.
5-40		(2*R*,5*R*)-*tert*-butyl 5-(cyanomethyl)-5-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate (from Example 5-36)	LRMS (ESI) calc'd for $C_{25}H_{30}N_5O_6S$ $[M+H]^+$: 528, found 528. LC retention time (IB column, 40% MeOH /EtOH = 3:2, 60% heptanes) = 9.6 minutes.
5-41		(2*S*,5*S*)-*tert*-butyl 5-(3-((2-(*tert*-butyl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-5-(cyanomethyl)tetrahydro-2*H*-pyran-2-carboxylate (from I-13-1A)	LRMS (ESI) calc'd for $C_{29}H_{37}N_6O_6S$ $[M+H]^+$: 597, found 597.
5-42		(2*R*,5*R*)-*tert*-butyl 5-(3-((2-(*tert*-butyl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-5-(cyanomethyl)tetrahydro-2*H*-pyran-2-carboxylate (from I-13-1B)	LRMS (ESI) calc'd for $C_{29}H_{37}N_6O_6S$ $[M+H]^+$: 597, found 597.

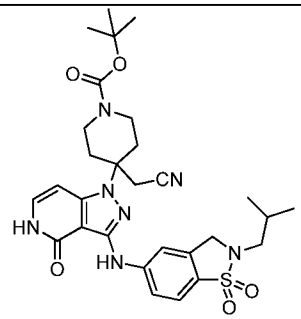
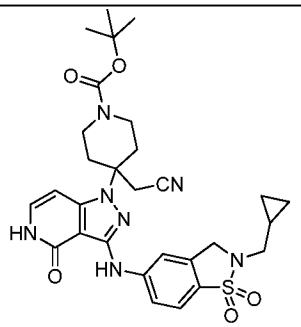
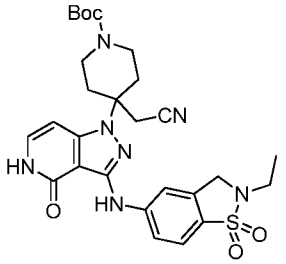
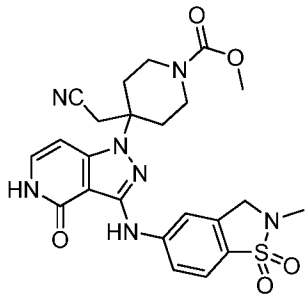
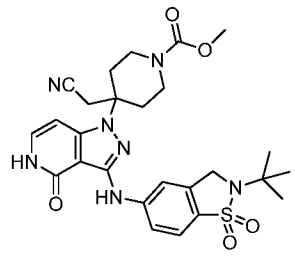
5-43		(2*S*,5*S*)-*tert*-butyl 5-(cyanomethyl)-5-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate (from I-13-1A)	LRMS (ESI) calc'd for $C_{26}H_{33}N_6O_6S$ $[M+H]^+$: 557, found 557.
5-44		(2*S*,5*S*)-*tert*-butyl 5-(cyanomethyl)-5-(3-((1,1-dioxido-2-(2,2,2-trifluoroethyl)-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate (from I-13-1A)	LRMS (ESI) calc'd for $C_{27}H_{30}F_3N_6O_6S$ $[M+H]^+$: 623, found 623.
5-45		*tert*-butyl 3-(cyanomethyl)-3-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)azetidine-1-carboxylate	LRMS (ESI) calc'd for $C_{18}H_{19}N_6O_3S$ $[M-Boc+H]^+$: 399, found 399.
5-46		*tert*-butyl 3-(cyanomethyl)-3-{3-[(2-fluoropyridin-4-yl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}azetidine-1-carboxylate	LRMS (ESI) calc'd for $C_{21}H_{23}FN_7O_3$ $[M+H]^+$: 440, found 440.
5-47		*tert*-butyl 3-(cyanomethyl)-3-[4-oxo-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]azetidine-1-carboxylate	LRMS (ESI) calc'd for $C_{23}H_{24}F_3N_6O_5S$ $[M+H]^+$: 553, found 553.

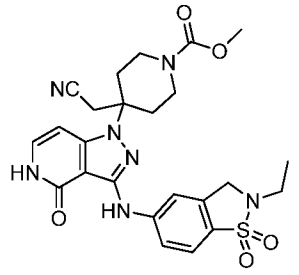
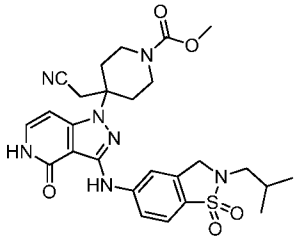
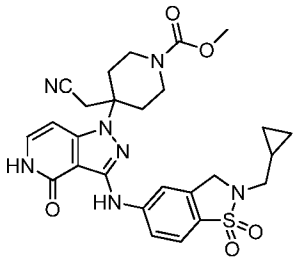
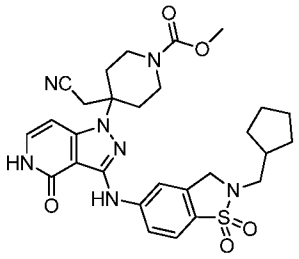
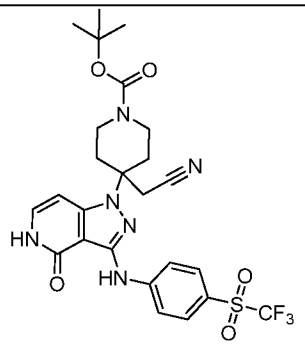
5-48		*tert*-butyl 4-(cyanomethyl)-4-{3-[(4-fluorophenyl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{24}H_{28}FN_6O_3$ $[M+H]^+$: 467, found 467.
5-49		*tert*-butyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)-3-methylphenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{22}H_{28}N_7O_3S$ $[M-Boc+H]^+$: 470, found 470.
5-50		(2*R*,5*S*)-*tert*-butyl 5-(3-((4-((*R or S*)-1-amino-2,2,2-trifluoroethyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-5-(cyanomethyl)tetrahydro-2H-pyran-2-carboxylate (from epimerized I-13-1A & I-23A)	LRMS (ESI) calc'd for $C_{26}H_{30}F_3N_6O_4$ $[M+H]^+$: 547, found 547.
5-51		(2*S*,5*S*)-*tert*-butyl 5-(3-((4-((*R or S*)-1-amino-2,2,2-trifluoroethyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-5-(cyanomethyl)tetrahydro-2H-pyran-2-carboxylate (from I-13-1A & I-23A)	LRMS (ESI) calc'd for $C_{26}H_{30}F_3N_6O_4$ $[M+H]^+$: 547, found 547.

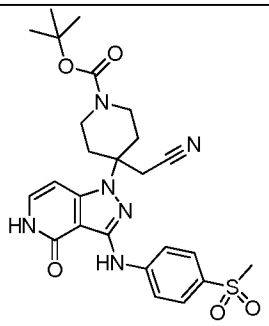
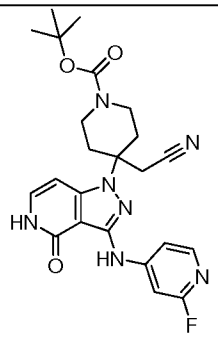
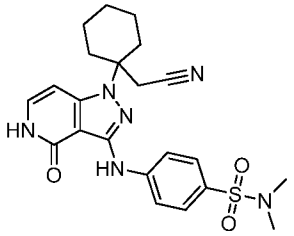
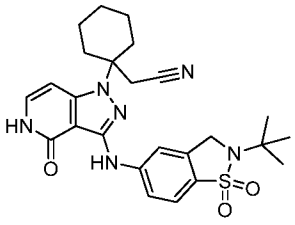
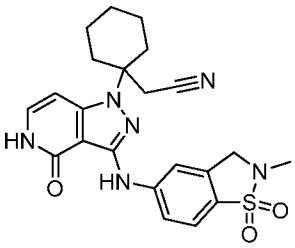
5-52		(2*R*,5*S*)-*tert*-butyl 5-(3-((4-((*S or R*)-1-amino-2,2,2-trifluoroethyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-5-(cyanomethyl)tetrahydro-2*H*-pyran-2-carboxylate (from epimerized I-13-1A & I-23B)	LRMS (ESI) calc'd for $C_{26}H_{30}F_3N_6O_4$ $[M+H]^+$: 547, found 547.
5-53		(2*S*,5*S*)-*tert*-butyl 5-(3-((4-((*S or R*)-1-amino-2,2,2-trifluoroethyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-5-(cyanomethyl)tetrahydro-2*H*-pyran-2-carboxylate (from I-13-1A & I-23B)	LRMS (ESI) calc'd for $C_{26}H_{30}F_3N_6O_4$ $[M+H]^+$: 547, found 547.
5-54		(2*S*,5*S*)-*tert*-butyl 5-(cyanomethyl)-5-(4-oxo-3-(phenylamino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate (from I-13-1A)	LRMS (ESI) calc'd for $C_{24}H_{28}N_5O_4$ $[M+H]^+$: 450, found 450.
5-55		(2*S*,5*S*)-*tert*-butyl 5-(cyanomethyl)-5-(3-((2-methyl-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate (from I-13-1A)	LRMS (ESI) calc'd for $C_{26}H_{31}N_6O_6S$ $[M+H]^+$: 555, found 555.
5-56		*N*-(*tert*-butyl)-4-((1-(4-(cyanomethyl)-1-(2,2-difluoropropanoyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)benzenesulfonamide	LRMS (ESI) calc'd for $C_{26}H_{32}F_2N_7O_4S$ $[M+H]^+$: 576, found 576.

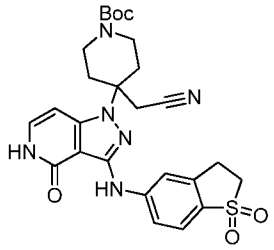
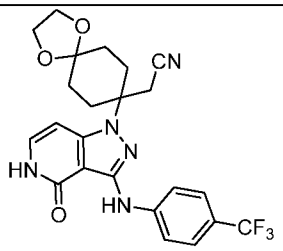
5-57		2-(1-(2,2-difluoropropanoyl)-4-(3-((4-(isopropylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidin-4-yl)acetonitrile	LRMS (ESI) calc'd for $C_{25}H_{29}F_2N_6O_4S$ $[M+H]^+$: 547, found 547.
5-58		*N*-(*tert*-butyl)-4-((1-(4-(cyanomethyl)-1-(2,2-difluoropropanoyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*-methylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{27}H_{33}F_2N_7O_4SNa$ $[M+Na]^+$: 612, found 612.
5-59		2-(4-(3-((4-(*tert*-butylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1-(2,2-difluoropropanoyl)piperidin-4-yl)acetonitrile	LRMS (ESI) calc'd for $C_{26}H_{30}F_2N_6O_4S$ $[M+H]^+$: 561, found 561.
5-60		*tert*-butyl 4-(3-(3,5-bis((1*H*-pyrazol-1-yl)methyl)phenylamino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{32}H_{37}N_{10}O_3$ $[M+H]^+$: 609, found 609.
5-61		*tert*-butyl 4-(cyanomethyl)-4-(3-(3,5-dimethylphenylamino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{26}H_{33}N_6O_3$ $[M+H]^+$: 477, found 477.

5-62		*tert*-butyl 4-(3-(3,5-bis((1*H*-1,2,3-triazol-1-yl)methyl)phenylamino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{30}H_{35}N_{12}O_3$ $[M+H]^+$: 611, found 611.
5-63		*tert*-butyl 4-(3-(3,5-bis((2*H*-1,2,3-triazol-2-yl)methyl)phenylamino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{30}H_{35}N_{12}O_3$ $[M+H]^+$: 611, found 611
5-64		*tert*-butyl 4-(3-(3-((1*H*-1,2,3-triazol-1-yl)methyl)-5-((2*H*-1,2,3-triazol-2-yl)methyl)phenylamino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{30}H_{35}N_{12}O_3$ $[M+H]^+$: 611, found 611.
5-65		*tert*-butyl 4-(3-(m-toluidino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{25}H_{31}N_6O_3$ $[M+H]^+$: 463, found 463.
5-66		*tert*-butyl 4-(cyanomethyl)-4-(3-(isoindolin-5-ylamino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{26}H_{32}N_7O_3$ $[M+H]^+$: 490, found 490.

5-67		1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl]amino}-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1- carboxylate	LRMS (ESI) calc'd for $C_{29}H_{38}N_7O_5S$ $[M+H]^+$: 596, found 596.
5-68		*tert*-butyl 4-(cyanomethyl)-4-(3-{[2-(cyclopropylmethyl)-1,1-dioxo-2,3-dihydro- 1,2-benzothiazol-5-yl]amino}-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1- carboxylate	MS (ESI) calc'd for $C_{29}H_{36}N_7O_5S$ $[M+H]^+$: 594, found 594.
5-69		*tert*-butyl 4-(cyanomethyl)-4-{3-[(2-ethyl-1,1- dioxo-2,3-dihydro-1,2-benzothiazol-5- yl)amino]-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{22}H_{26}N_7O_3S$ $[M-Boc+H]^+$: 468, found 468.
5-70		methyl 4-(cyanomethyl)-4-[3-[(2-methyl-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl)amino]-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{23}H_{26}N_7O_5S$ $[M+H]^+$: 512, found 512.
5-71		methyl 4-{3-[(2-*tert*-butyl-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl)amino]-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl}-4-(cyanomethyl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{26}H_{32}N_7O_5S$ $[M+H]^+$: 554, found 554.

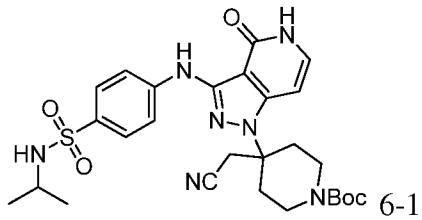
5-72		methyl 4-{3-[(2-ethyl-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl)amino]-4-oxo-1H,4H,5H-pyrazolo[4,3-c]pyridin-1-yl}-4-(cyanomethyl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{24}H_{28}N_7O_5S$ $[M+H]^+$: 526, found 526.
5-73		methyl 4-(cyanomethyl)-4-(3-{[2-(2-methylpropyl)-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl]amino}-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{26}H_{32}N_7O_5S$ $[M+H]^+$: 554, found 554.
5-74		methyl 4-(cyanomethyl)-4-(3-{[2- (cyclopropylmethyl)-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl]amino}-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{26}H_{30}N_7O_5S$ $[M+H]^+$: 552, found 552.
5-75		methyl 4-(cyanomethyl)-4-(3-{[2-(cyclopentylmethyl)-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl]amino}-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{28}H_{34}N_7O_5S$ $[M+H]^+$: 580, found 580.
5-76		*tert*-butyl 4-(cyanomethyl)-4-[4-oxo-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{25}H_{28}F_3N_6O_5S$ $[M+H]^+$: 581, found 525.

5-77		*tert*-butyl 4-(cyanomethyl)-4-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{20}H_{23}N_6O_3S$ $[M\text{-}Boc+H]^+$: 427, found 427.
5-78		*tert*-butyl 4-(cyanomethyl)-4-{3-[(2-fluoropyridin-4-yl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{23}H_{27}FN_7O_3$ $[M+H]^+$: 468, found 468.
5-79		4-(1-(1-(cyanomethyl)cyclohexyl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-c]pyridin-3-ylamino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{22}H_{27}N_6O_3S$ $[M+H]^+$: 455, found 455.
5-80		2-(1-(3-((2-(*tert*-butyl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{25}H_{31}N_6O_3S$ $[M+H]^+$: 495, found 495.
5-81		2-(1-(3-((2-methyl-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{22}H_{25}N_6O_3S$ $[M+H]^+$: 453, found 453.

5-82		*tert*-butyl 4-(cyanomethyl)-4-(3-((1,1-dioxido-2,3-dihydrobenzo[*b*]thiophen-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{26}H_{31}N_6O_5S$ $[M+H]^+$: 539, found 539.
5-83		2-(8-(4-oxo-3-((4-(trifluoromethyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1,4-dioxaspiro[4.5]decan-8-yl)acetonitrile	LRMS (ESI) calc'd for $C_{30}H_{28}F_3N_5O_3$ $[M+H]^+$: 474, found 474.

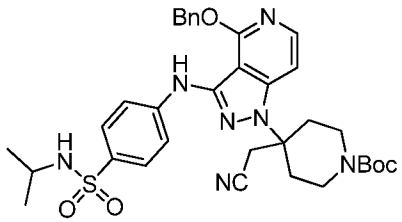
Example 6-1

tert-butyl 4-(cyanomethyl)-4-(3-((4-(*N*-isopropylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate



6-1

Step 1: *tert*-butyl 4-(4-(benzyloxy)-3-((4-(*N*-isopropylsulfamoyl)phenyl)amino)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate



6-1a

To a suspension of *tert*-butyl 4-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate (0.11 g, 0.25 mmol) and KOAc (50 mg, 0.10 mmol) in *i*-PrOH (1.0 ml) under nitrogen, was added 4-bromo-*N*- isopropylbenzene-sulfonamide (0.11 g, 0.40 mmol), $Pd_2(dba)_3$ (23 mg, 0.025 mmol) and 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (11 mg, 0.026 mmol). The resulting suspension was heated to 105 °C by microwave irradiation for 1 hour, then cooled and filtered. The filtrate was concentrated

in vacuo, and the residue was purified by preparative TLC to give the desired compound, 6-1a, as a white solid. LRMS (ESI) calc'd for $C_{34}H_{42}N_7O_5S$ $[M+H]^+$: 660, found 660.

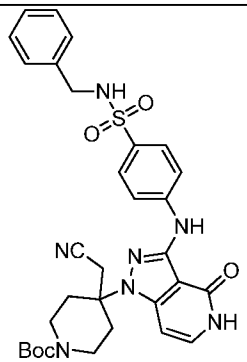
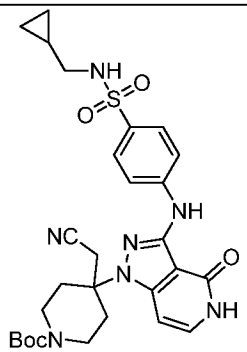
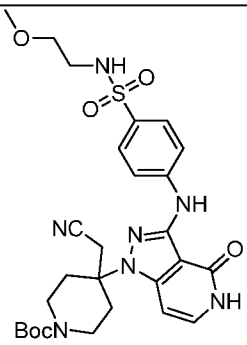
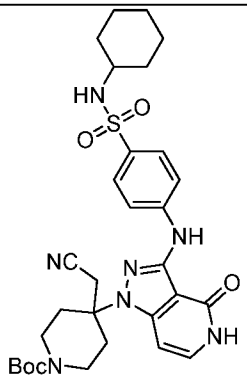
Step 2: *tert*-butyl 4-(cyanomethyl)-4-(3-((4-(*N*-isopropylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate

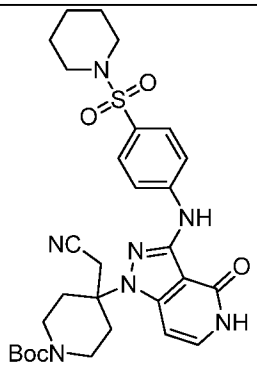
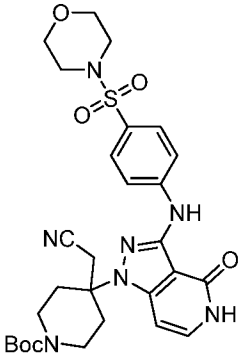
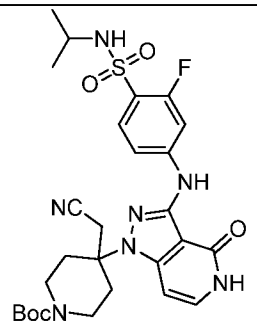
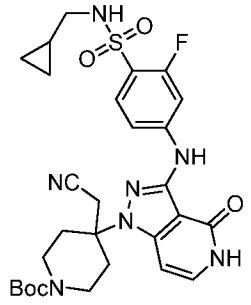
To a suspension of compound *tert*-butyl 4-(4-(benzyloxy)-3-((4-(*N*-isopropylsulfamoyl)phenyl)amino)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate (6-1a) (80 mg, 0.12 mmol) in EtOH (2.0 mL) was added 10 wt.% Pd/C (20 mg). The resulting suspension was stirred for 24 hours at room temperature under 1 atmosphere of hydrogen. The reaction mixture was then filtered through Celite, and the filtrate was concentrated *in vacuo*. The residue was then purified by reverse phase HPLC using acetonitrile/water with 0.225% formic acid as modifier, to afford compound 6-1 as a white solid. LRMS (ESI) calc'd for $C_{27}H_{36}N_7O_5S$ $[M+H]^+$: 570, found 570. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.36 (s, 1H), 8.62 (s, 1H), 7.80 (d, J = 9.2 Hz, 2H), 7.70 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 7.2 Hz, 1H), 7.20 (d, J = 7.6Hz, 1H), 6.70 (d, J = 7.6 Hz, 1H), 3.77–3.73 (m, 2H), 3.33 (s, 2H), 3.22–3.18 (m, 2H), 3.15–3.05 (m, 2H), 2.71–2.70 (m, 1H), 2.52–2.49 (m, 1H), 2.08–2.01 (m, 2H),1.40 (s, 9H), 0.96 (d, J = 6.4 Hz, 6H).

Following an analogous procedure to that outlined above for Example 6-1, the following additional examples in Table 11 were prepared:

Table 11:

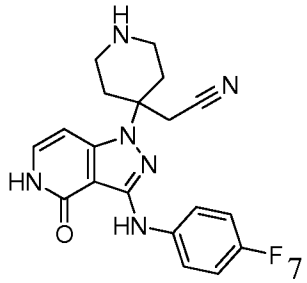
Example	Structure	Compound Name	LRMS

6-2		*tert*-butyl 4-(3-((4-(*N*-benzylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{26}H_{28}N_7O_3S$ [M-Boc+H]$^+$: 518, found 518.
6-3		*tert*-butyl 4-(cyanomethyl)-4-(3-((4-(*N*-(cyclopropylmethyl)sulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{23}H_{28}N_7O_3S$ [M-Boc+H]$^+$: 482, found 482.
6-4		*tert*-butyl 4-(cyanomethyl)-4-(3-((4-(*N*-(2-methoxyethyl)sulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{22}H_{28}N_7O_4S$ [M-Boc+H]$^+$: 486, found 486.
6-5		*tert*-butyl 4-(cyanomethyl)-4-(3-((4-(*N*-cyclohexylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{30}H_{40}N_7O_5S$ [M+H]$^+$: 610, found 610.

6-6		*tert*-butyl 4-(cyanomethyl)-4-(4-oxo-3-((4-(piperidin-1-ylsulfonyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{29}H_{38}N_7O_5S$ $[M+H]^+$: 596, found 596.
6-7		*tert*-butyl 4-(cyanomethyl)-4-(3-((4-(morpholinosulfonyl) phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{28}H_{36}N_7O_6S$ $[M+H]^+$: 598, found 598.
6-8		*tert*-butyl 4-(cyanomethyl)-4-(3-((3-fluoro-4-(*N*-isopropylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{27}H_{34}FN_7O_5SNa$ $[M+Na]^+$: 610, found 610.
6-9		*tert*-butyl 4-(cyanomethyl)-4-(3-((4-(*N*-(cyclopropylmethyl)sulfamoyl)-3-fluorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{28}H_{34}FN_7O_5SNa$ $[M+Na]^+$: 622, found 622.

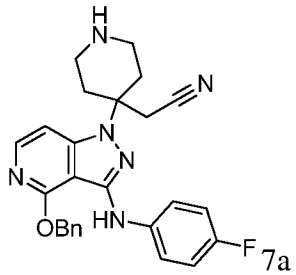
Example 7

(4-{3-[(4-fluorophenyl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidin-4-yl)acetonitrile



7

Step 1: (4-{4-(benzyloxy)-3-[(4-fluorophenyl)amino]-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidin-4-yl)acetonitrile



7a

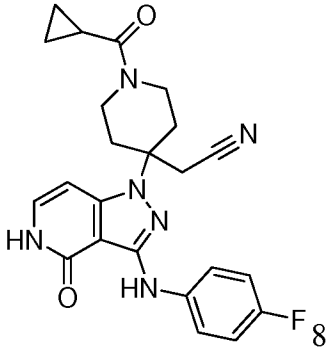
To a solution of *tert*-butyl 4-{4-(benzyloxy)-3-[(4-fluorophenyl)amino]-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}-4-(cyanomethyl)piperidine-1-carboxylate (Example 5-48, step 1) (32 mg, 0.057 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.10 mL, 1.3 mmol). The reaction was stirred at room temperature for 30 minutes, diluted with EtOAc, and then washed with 1N NaOH and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Crude 7a, was used as is in the next step. LRMS (ESI) calc'd for $C_{26}H_{26}FN_6O$ $[M+H]^+$: 457, found 457.

Step 2: (4-{3-[(4-fluorophenyl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidin-4-yl)acetonitrile

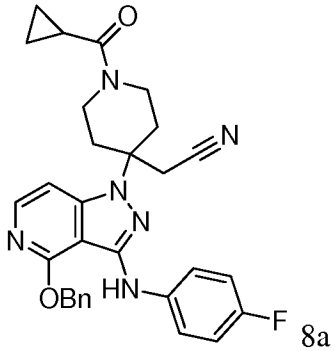
To a solution of crude 7a (28 mg, 0.061 mmol) in EtOAc (0.5 mL) and EtOH (0.5 mL) was added 10% wt. Pd/C (5 mg). The reaction was placed under 1 atmosphere of hydrogen and stirred vigorously at room temperature for 2 hours. The hydrogen atmosphere was removed and then the catalyst was removed by filtration through Celite. The filtrate was concentrated *in vacuo* and the residue was purified by mass triggered reverse phase HPLC, eluting with acetonitrile/water containing 0.1% TFA modifier. Fractions containing desired product were lyophilized to afford compound 7 as the TFA salt. LRMS (ESI) calc'd for $C_{19}H_{20}FN_6O$ $[M+H]^+$: 367, found 367. ^1H NMR (600 MHz, DMSO-*d6*): δ 11.35 (d, J = 6.0 Hz, 1H), 8.40–8.55 (m, 2H), 8.20 (s, 1H), 7.63 (m, 2H), 7.21 (t, J = 6.6 Hz, 1H), 7.07 (t, J = 8.4 Hz, 2H), 6.66 (d, J = 7.2 Hz, 1H), 3.26–3.34 (m, 4H), 2.97 (m, 2H), 2.82 (m, 2H), 2.19 (m, 2H).

Example 8

[1-(cyclopropylcarbonyl)-4-{3-[(4-fluorophenyl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidin-4-yl]acetonitrile



Step 1: [4-{4-(benzyloxy)-3-[(4-fluorophenyl)amino]-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}-1-(cyclopropylcarbonyl)piperidin-4-yl]acetonitrile



To a solution of crude (4-{4-(benzyloxy)-3-[(4-fluorophenyl)amino]-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidin-4-yl)acetonitrile (7a) (21 mg, 0.046 mmol) in CH_2Cl_2 (1.0 mL) was added DIPEA (24.0 μL, 0.138 mmol) followed by cyclopropanecarbonyl chloride (6.3 μL, 0.069 mmol). The reaction was stirred at room temperature for 30 minutes and then diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue using silica chromatography, eluting with 0–100% EtOAc in hexanes afforded 8a. LRMS (ESI) calc'd for $C_{30}H_{30}FN_6O_2$ $[M+H]^+$: 525, found 525.

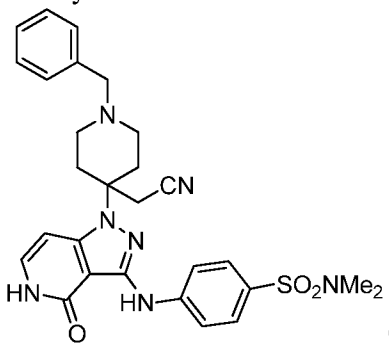
Step 2: [1-(cyclopropylcarbonyl)-4-{3-[(4-fluorophenyl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidin-4-yl]acetonitrile

To a solution of compound 8a (12 mg, 0.024 mmol) in EtOAc (1.5 mL) and EtOH (0.5 mL) was added 10 wt.% Pd/C (5.0 mg). The reaction was placed under 1 atmosphere of hydrogen and stirred vigorously at room temperature for 2 hours. The hydrogen atmosphere was removed and the reaction was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was purified by silica chromatography, eluting with 0–5% MeOH in EtOAc to afford compound 8. LRMS (ESI) calc'd for $C_{23}H_{24}FN_6O_2$ $[M+H]^+$: 435, found 435. ^1H NMR (600 MHz, CD_3OD): δ 8.06 (s, 1H), 7.60 (m, 2H), 7.19 (d, J = 7.2 Hz, 1H), 7.01 (t, J = 8.4 Hz,

2H), 6.73 (d, J = 7.8 Hz, 1H), 5.47 (s, 1H), 4.25 (m, 2H), 3.51 (m, 1H), 3.14 (s, 2H), 2.86–3.15 (m, 3H), 1.95–2.18 (m, 3H), 0.74–0.90 (m, 4H).

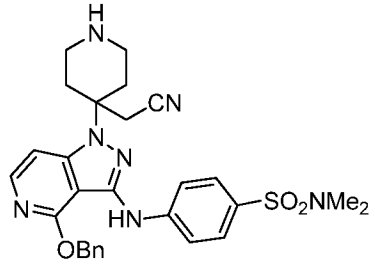
Example 9-1

4-({1-[1-benzyl-4-(cyanomethyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide



9-1

Step 1: 3-((4-(benzyloxy)-1-(4-(cyanomethyl)piperidin-4-yl)-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide



9-1a

To a solution of *tert*-butyl 4-(4-(benzyloxy)-3-((3-(*N*,*N*-dimethylsulfamoyl) phenyl)amino)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate (3.50 g, 5.42 mmol) in CH_2Cl_2 (46 mL) at 0 °C, tetrafluoroboric acid-diethyl ether complex (1.55 mL, 11.4 mmol) was added. The reaction mixture was stirred and warmed to room temperature over 4 hours. The reaction was quenched with saturated aqueous $NaHCO_3$, and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (× 3). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford compound 9-1a as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, J = 6.5 Hz, 1H), 7.73–7.70 (m, 3H), 7.56–7.44 (m, 6 H), 6.98 (d, J = 6.5 Hz, 1H), 5.60 (s, 2H), 3.21–3.10 (m, 2H), 3.02–2.96 (m, 6H), 2.69 (s, 6H), 2.28–2.24 (m, 2H).

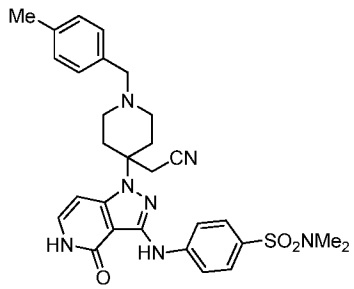
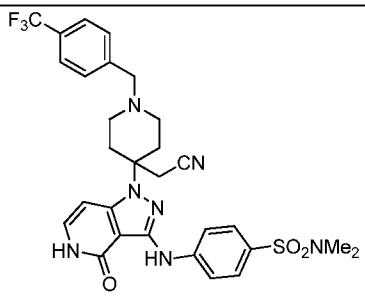
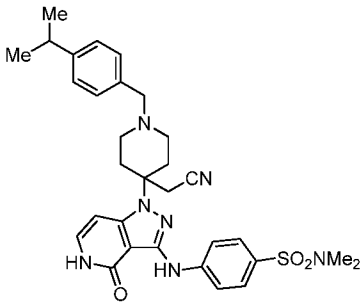
Step 2: 4-({1-[1-benzyl-4-(cyanomethyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*dimethylbenzenesulfonamide

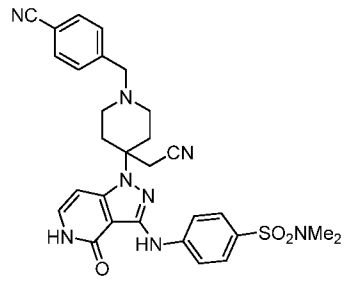
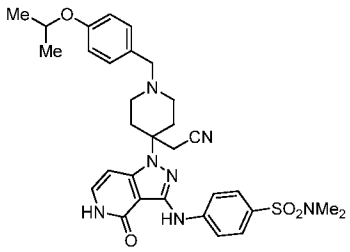
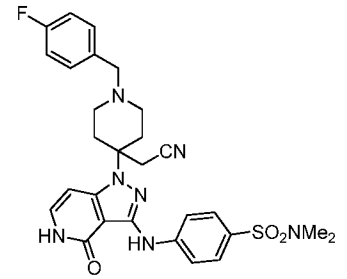
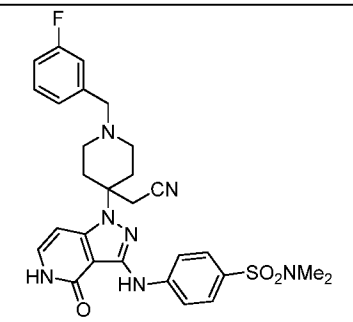
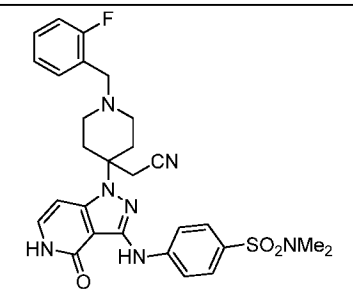
An oven dried reaction vessel was charged with compound 9-1a (20 mg, 0.037 mmol), DMF (0.19 mL, 0.2 M), benzaldehyde (3.8 mg, 0.037 mmol), TFA (18.8 mg, 0.165 mmol), and triacetoxyborohydride (39 mg, 0.183 mmol). The reaction vessel was sealed and

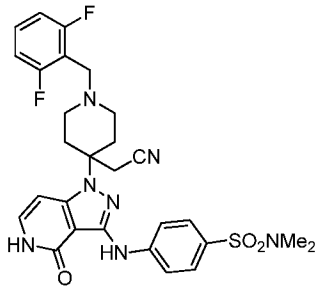
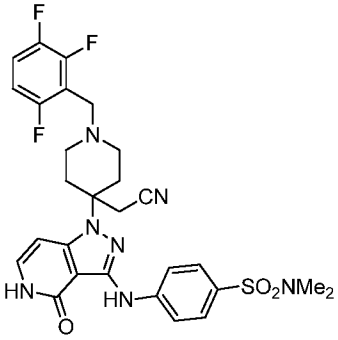
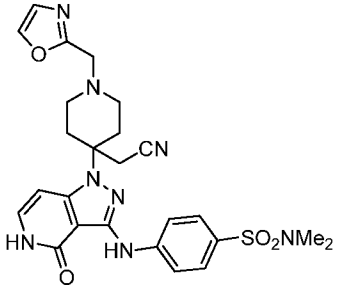
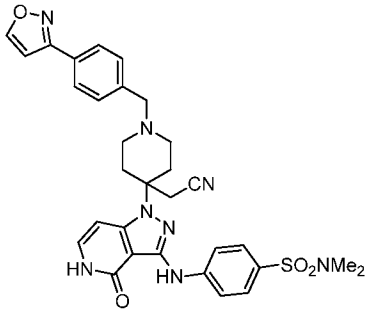
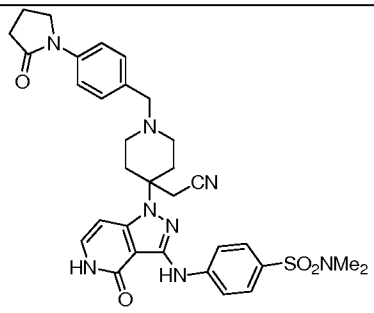
heated to 50 °C overnight. Upon cooling to room tempearture, HCl in dioxane (0.10 mL, 2M) was added, and the reaction mixture was stirred for an additional 4 hours. The crude reaction mixture was filtered and purified using mass directed reverse phase column chromatography to afford Example 9-1. LRMS (ESI) calc'd for $C_{28}H_{32}N_7O_3S$ [M+H]+: 546, found 546. ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.31 (s, 1H) 8.68 (s, 1H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.26 (m, 3H), 7.18 (m, 1H), 7.16 (m, 1H), 6.67 (m, 1H), 6.51 (m, 1H), 3.71 (br s, 1H), 2.65 (d, 2H), 2.54 (s, 6H), 2.08 (m, 1H), 1.36 (s, 2H).

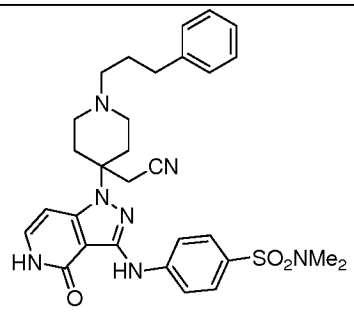
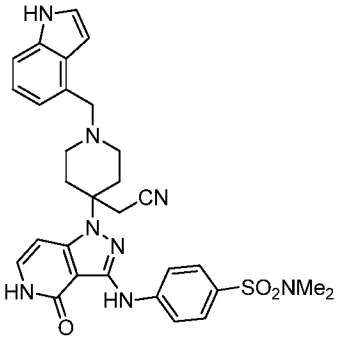
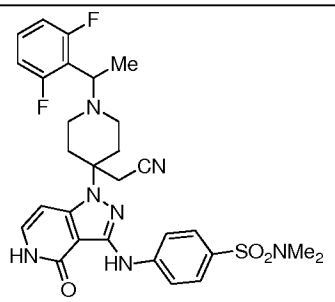
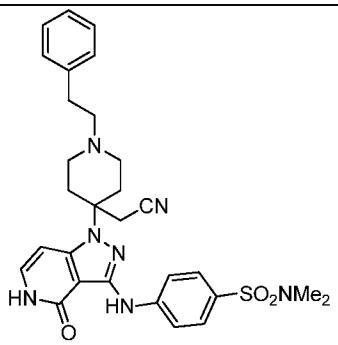
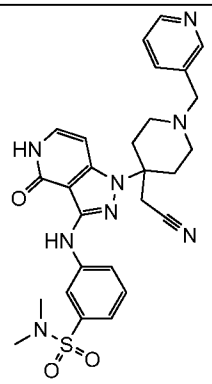
The following compounds in Table 12 were prepared in analogy to Example 9-1 above.

Table 12

Example	Structure / Name	Compound Name	LRMS
9-2		4-({1-[4-(cyanomethyl)-1-(4-methylbenzyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzene sulfonamide	LRMS (ESI) calc'd for $C_{29}H_{34}N_7O_3S$ $[M+H]^+$: 560, found 560.
9-3		4-[(1-{4-(cyanomethyl)-1-[4-(trifluoromethyl) benzyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethyl benzenesulfonamide	LRMS (ESI) calc'd for $C_{29}H_{31}F_3N_7O_3S$ $[M+H]^+$: 614, found 614.
9-4		4-[(1-{4-(cyanomethyl)-1[4-(1-methylethyl) benzyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzene sulfonamide	LRMS (ESI) calc'd for $C_{31}H_{38}N_7O_3S$ $[M+H]^+$: 588, found 588.

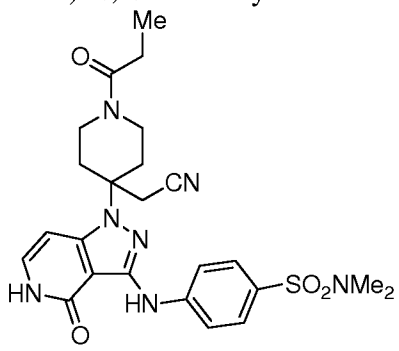
9-5		4-[(1-{4-(cyanomethyl)-1-[4-(1-methylethyl)benzyl] piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzene sulfonamide	LRMS (ESI) calc'd for $C_{29}H_{31}N_8O_3S$ $[M+H]^+$: 571, found 571.
9-6		4-[(1-{4-(cyanomethyl)-1-[4-(1methylethoxy)benzyl] piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzene sulfonamide	LRMS (ESI) calc'd for $C_{31}H_{38}N_7O_4S$ $[M+H]^+$: 604, found 604.
9-7		4-({1-[4-(cyanomethyl)-1-(4-fluorobenzyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzene sulfonamide	LRMS (ESI) calc'd for $C_{28}H_{31}FN_7O_3S$ $[M+H]^+$: 564, found 564.
9-8		4-({1-[4-(cyanomethyl)-1-(3-fluorobenzyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzene sulfonamide	LRMS (ESI) calc'd for $C_{28}H_{31}FN_7O_3S$ $[M+H]^+$: 564, found 564.
9-9		4-({1-[4-(cyanomethyl)-1-(2-fluorobenzyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzene sulfonamide	LRMS (ESI) calc'd for $C_{28}H_{31}FN_7O_3S$ $[M+H]^+$: 564, found 564.

9-10		4-({1-[4-(cyanomethyl)-1-(2,6-difluorobenzyl) piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N,N*-dimethylbenzene sulfonamide	LRMS (ESI) calc'd for $C_{28}H_{30}F_2N_7O_3S$ $[M+H]^+$: 582, found 582.
9-11		4-({1-[4-(cyanomethyl)-1-(2,3,6-trifluorobenzyl) piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N,N*-dimethylbenzene sulfonamide	LRMS (ESI) calc'd for $C_{28}H_{29}F_3N_7O_3S$ $[M+H]^+$: 600, found 600.
9-12		4-({1-[4-(cyanomethyl)-1-(1,3-oxazol-2-ylmethyl) piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N,N*-dimethylbenzene sulfonamide	LRMS (ESI) calc'd for $C_{25}H_{29}N_8O_4S$ $[M+H]^+$: 537, found 537.
9-13		4-({1-[4-(cyanomethyl)-1-(4-isoxazol-3-ylbenzyl) piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N,N*-dimethylbenzene sulfonamide	LRMS (ESI) calc'd for $C_{31}H_{33}N_8O_4S$ $[M+H]^+$: 613, found 613.
9-14		4-[(1-{4-(cyanomethyl)-1-[4-(2-oxopyrrolidin-1-yl)benzyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N,N*-dimethylbenzene sulfonamide	LRMS (ESI) calc'd for $C_{32}H_{37}N_8O_4S$ $[M+H]^+$: 629, found 629.

9-15		4-({1-[4-(cyanomethyl)-1-(3-phenylpropyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N,N*-dimethylbenzene sulfonamide	LRMS (ESI) calc'd for $C_{30}H_{36}N_7O_3S$ $[M+H]^+$: 574, found 574.
9-16		4-({1-[4-(cyanomethyl)-1-(1*H*-indol-4-ylmethyl) piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N,N*-dimethylbenzene sulfonamide	LRMS (ESI) calc'd for $C_{30}H_{33}N_8O_3S$ $[M+H]^+$: 585, found 585.
9-17		4-((1-(4-(cyanomethyl)-1-(1-(2,6-difluorophenyl) ethyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N,N*-dimethyl benzenesulfonamide	LRMS (ESI) calc'd for $C_{29}H_{32}F_2N_7O_3S$ $[M+H]^+$: 596, found 596.
9-18		4-((1-(4-(cyanomethyl)-1-phenethylpiperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N,N*-dimethylbenzene sulfonamide	LRMS (ESI) calc'd for $C_{29}H_{34}N_7O_3S$ $[M+H]^+$: 560, found 560.
9-19		3-({1-[4-(cyanomethyl)-1-(pyridin-3-ylmethyl) piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N,N*-dimethylbenzene sulfonamide	LRMS (ESI) calc'd for $C_{27}H_{31}N_8O_3S$ $[M+H]^+$: 547, found 547.

Example 10-1

4-({1-[4-(cyanomethyl)-1-propanoylpiperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide

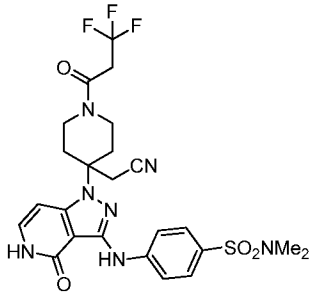


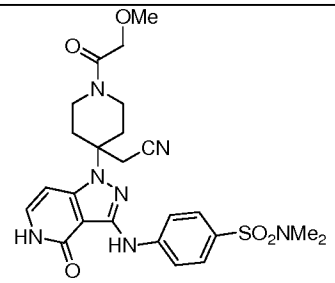
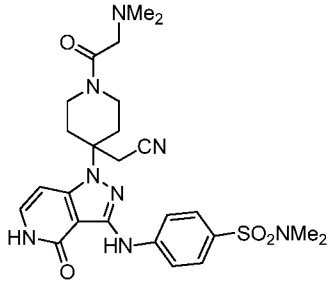
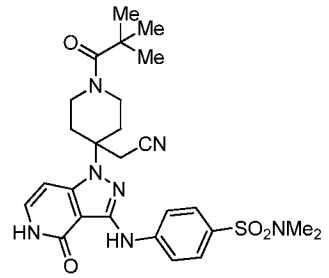
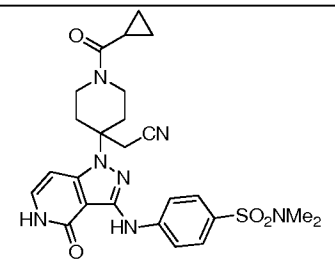
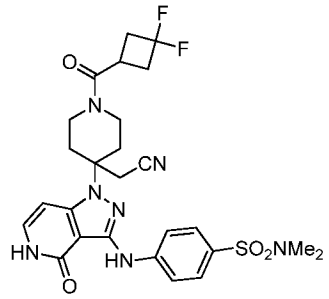
10-1

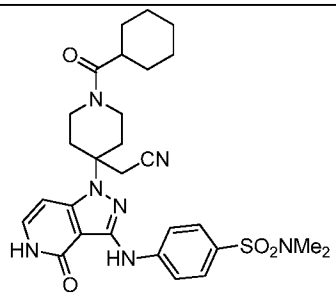
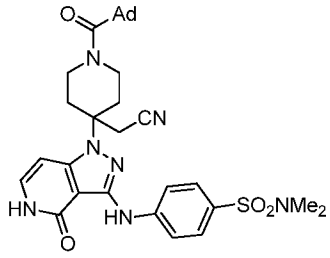
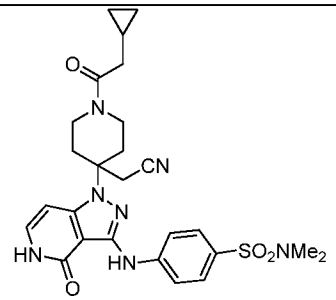
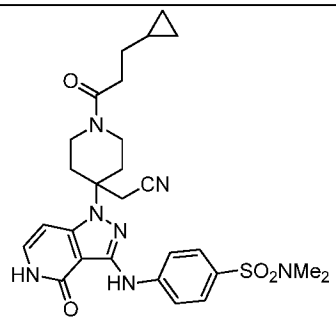
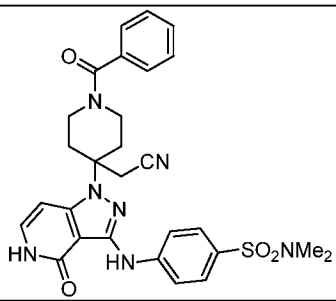
An oven dried reaction vessel was charged with PS-CDI (97 mg, 0.137 mmol) and DMF (0.55 mL, 0.1 M), and was shaken for 5 minutes. To this suspension, HOBt (11 mg, 0.082 mmol), 3-((4-(benzyloxy)-1-(4-(cyanomethyl)piperidin-4-yl)-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide (9-1a) (30 mg, 0.055 mmol), and propionic acid (4.1 mg, 0.055 mmol) were added followed by DIPEA (14 mg, 0.11 mmol). The reaction mixture was stirred at room temperature overnight, then HCl in dioxane (0.20 mL, 2M) was added, and the reaction mixture was stirred at room tempearture for an additional 2 hours. To this reaction mixture, Si-Carbonate (250 mg, 0.11 mmol) and additional DMF (1.0 mL) were added. The reaction was stirred overnight at room temperature. The reaction mixture was filtered, and the crude material containing compound 10-1 was purified using mass directed reverse phase column chromatography. LRMS (ESI) calc'd for $C_{24}H_{30}N_7O_4S$ [M+H]+: 512, found 512. ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.33 (d, *J* = 5.9 Hz, 1H), 8.68 (s, 1H), 7.83 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.19 (t, *J* = 6.7 Hz, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 4.00 (m, 1H), 3.73 (m, 1H), 3.29–3.23 (m, 3H), 3.05–3.01 (m, 1H), 2.69–2.65 (m, 2H), 2.54 (s, 6H), 2.34–2.30 (m, 2H), 2.05 (m, 1H), 1.96 (m, 1H), 0.94 (t, *J* = 7.4 Hz, 3H).

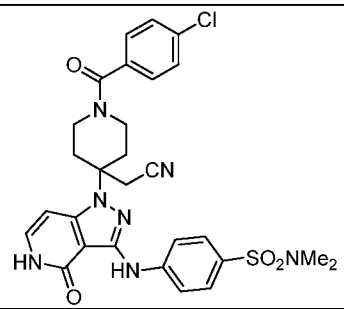
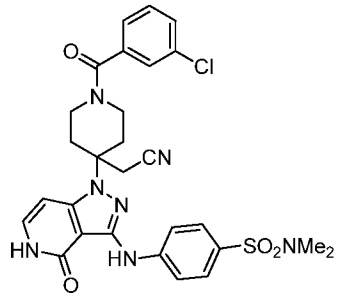
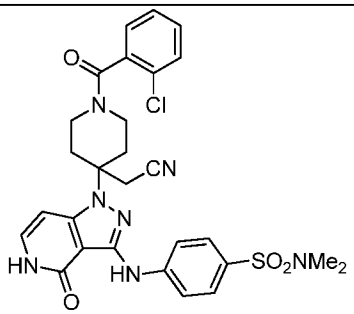
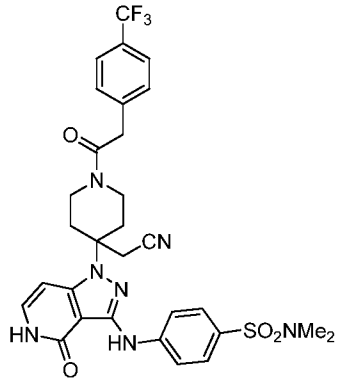
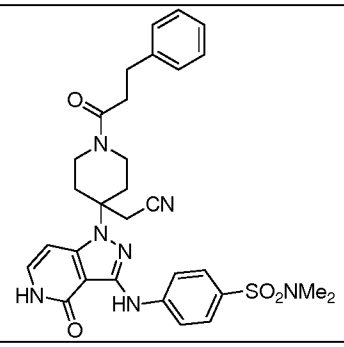
The following compounds in Table 13 were prepared in analogy to compound 10-1.

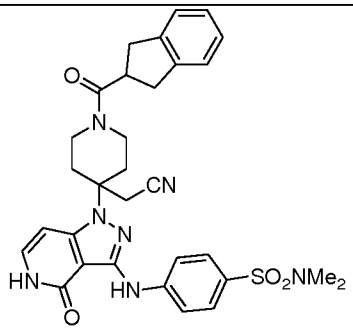
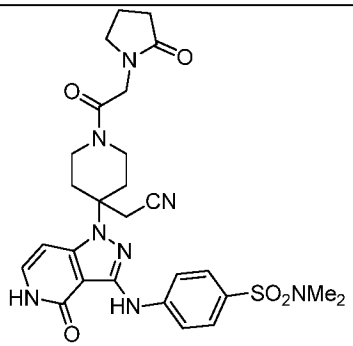
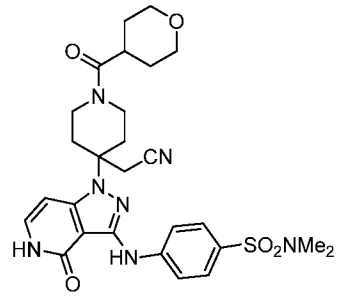
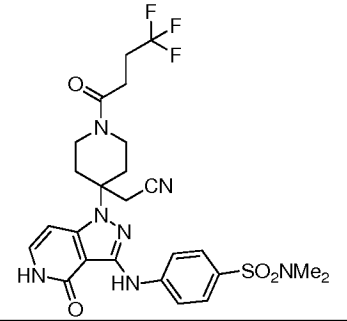
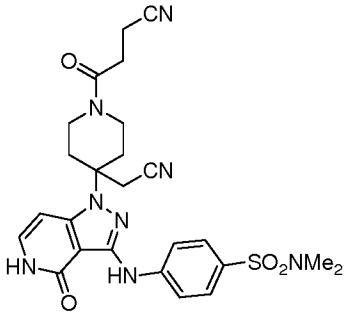
Table 13

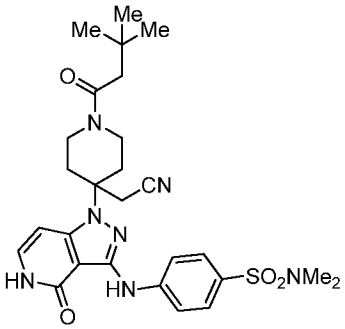
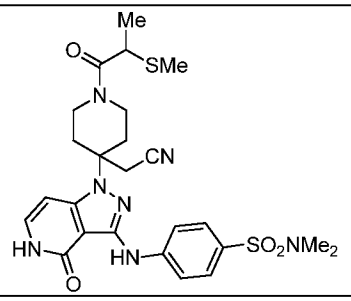
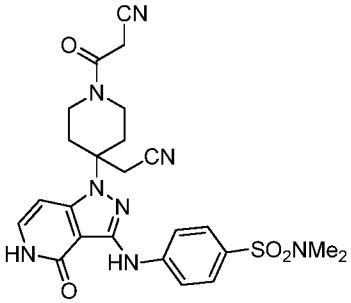
Example	Structure	Compound Name	LRMS
10-2		4-({1-[4-(cyanomethyl)-1-(3,3,3-trifluoropropanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{24}H_{27}F_3N_7O_4S$ $[M+H]^+$: 566, found 566.

10-3		4-({1-[4-(cyanomethyl)-1-(methoxyacetyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{24}H_{30}N_7O_5S$ $[M+H]^+$: 528, found 528.
10-4		4-({1-[4-(cyanomethyl)-1-(*N*,*N*-dimethylglycyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{25}H_{33}N_8O_4S$ $[M+H]^+$: 541, found 541.
10-5		4-({1-[4-(cyanomethyl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{26}H_{34}N_7O_4S$ $[M+H]^+$: 540, found 540.
10-6		4-({1-[4-(cyanomethyl)-1-(cyclopropylcarbonyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{26}H_{30}N_7O_4S$ $[M+H]^+$: 524, found 524.
10-7		4-[(1-{4-(cyanomethyl)-1-[(3,3-difluorocyclobutyl)carbonyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{26}H_{30}F_2N_7O_4S$ $[M+H]^+$: 574, found 574.

10-8		4-({1-[4-(cyanomethyl)-1-(cyclohexylcarbonyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{28}H_{36}N_7O_4S$ $[M+H]^+$: 566, found 566.
10-9		4-[(1-{4-(cyanomethyl)-1-[(3*S*,5*S*,7*S*)-tricyclo[3.3.1.1^{3,7}]dec-1-ylcarbonyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{32}H_{40}N_7O_4S$ $[M+H]^+$: 618, found 618.
10-10		4-({1-[4-(cyanomethyl)-1-(cyclopropylacetyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{26}H_{32}N_7O_4S$ $[M+H]^+$: 538, found 538.
10-11		4-({1-[4-(cyanomethyl)-1-(3-cyclopropylpropanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{27}H_{34}N_7O_4S$ $[M+H]^+$: 552, found 552.
10-12		4-({1-[4-(cyanomethyl)-1-(phenylcarbonyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{28}H_{30}N_7O_4S$ $[M+H]^+$: 560, found 560.

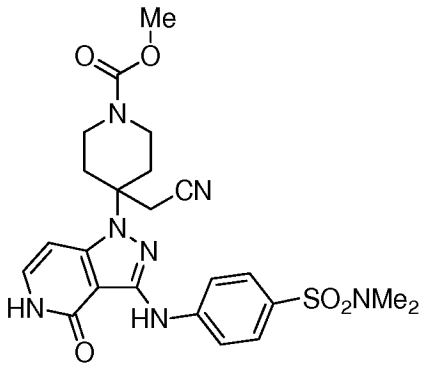
10-13		4-[(1-{1-[(4-chlorophenyl)carbonyl]-4-(cyanomethyl)piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{28}H_{29}ClN_7O_4S$ $[M+H]^+$: 594, found 594.
10-14		4-[(1-{1-[(3-chlorophenyl)carbonyl]-4-(cyanomethyl)piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{28}H_{29}ClN_7O_4S$ $[M+H]^+$: 594, found 594.
10-15		4-[(1-{1-[(2-chlorophenyl)carbonyl]-4-(cyanomethyl)piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{28}H_{29}ClN_7O_4S$ $[M+H]^+$: 594, found 594.
10-16		4-({1-[4-(cyanomethyl)-1-{[4-(trifluoromethyl)phenyl]acetyl}piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{30}H_{31}F_3N_7O_4S$ $[M+H]^+$: 642, found 642.
10-17		4-({1-[4-(cyanomethyl)-1-(3-phenylpropanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{30}H_{34}N_7O_4S$ $[M+H]^+$: 588, found 588.

10-18		4-({1-[4-(cyanomethyl)-1-(2,3-dihydro-1*H*-inden-2-ylcarbonyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{31}H_{34}N_7O_4S$ $[M+H]^+$: 600, found 600.
10-19		4-[(1-{4-(cyanomethyl)-1-[(2-oxopyrrolidin-1-yl)acetyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{27}H_{33}N_8O_5S$ $[M+H]^+$: 581, found 581.
10-20		4-({1-[4-(cyanomethyl)-1-(tetrahydro-2*H*-pyran-4-ylcarbonyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{27}H_{34}N_7O_5S$ $[M+H]^+$: 568, found 568.
10-21		4-({1-[4-(cyanomethyl)-1-(4,4,4-trifluorobutanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{25}H_{29}F_3N_7O_4S$ $[M+H]^+$: 580, found 580.
10-22		4-({1-[4-(cyanomethyl)-1-(3-cyanopropanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{25}H_{29}N_8O_4S$ $[M+H]^+$: 537, found 537.

10-23		4-({1-[4-(cyanomethyl)-1-(3,3-dimethylbutanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{27}H_{36}N_7O_4S$ $[M+H]^+$: 554, found 554.
10-24		4-((1-(4-(cyanomethyl)-1-(2-(methylthio)propanoyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{25}H_{32}N_7O_4S_2$ $[M+H]^+$: 558, found 558.
10-25		4-((1-(1-(2-cyanoacetyl)-4-(cyanomethyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{24}H_{27}N_8O_4S$ $[M+H]^+$: 523, found 523.

Example 11-1

methyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate



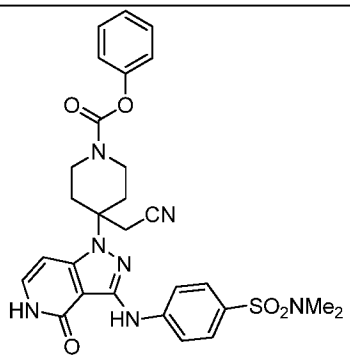
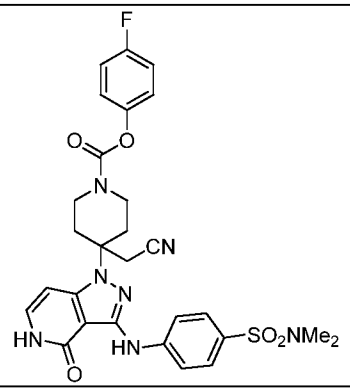
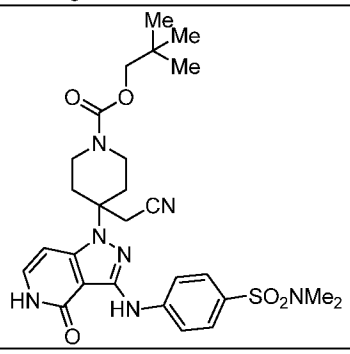
11-1

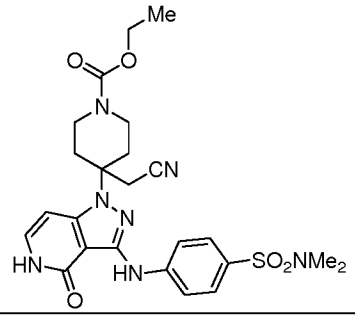
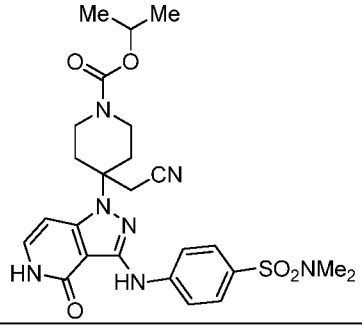
To a solution of 3-((4-(benzyloxy)-1-(4-(cyanomethyl)piperidin-4-yl)-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide (9-1a) (25 mg, 0.046 mmol), in CH_2Cl_2 (0.2 M), was added 2,6-lutidine (12.3 mg, 0.115 mmol). The reaction mixture

was cooled to 0 °C and methyl chloroformate (4.76 mg, 0.050 mmol) was added. The reaction was stirred to room temperature until the reaction was judged complete by LCMS, at which point it was cooled to 0 °C and 0.2 mL of TFA was added. The reaction mixture was filtered and purified using mass directed reverse phase column chromatography. LRMS (ESI) calc'd for $C_{23}H_{28}N_7O_5S$ [M+H]+: 514, found 514. ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.33 (d, *J* = 5.9 Hz, 1H), 8.71 (s, 1H), 7.85 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.19 (m, 1H), 6.70 (m, 1H), 3.82–3.78 (m, 2H), 3.58 (s, 3H), 3.31 (m, 1H), 3.29 (m, 1H), 3.21–3.13 (m, 1H), 2.72–2.64 (m, 1H), 2.57 (s, 6H), 2.48–2.44 (m, 2H), 2.10–2.02 (m, 2H).

The following compounds in Table 14 were prepared in analogy to that of Example 11-1.

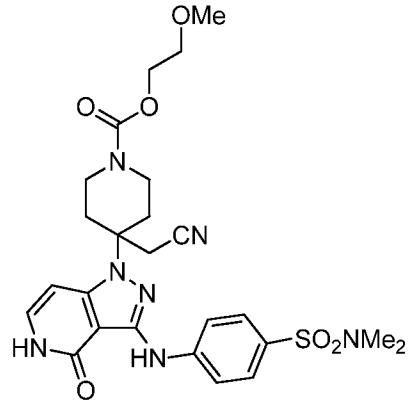
Table 14

Example	Structure	Compound Name	LRMS
11-2		phenyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{28}H_{30}N_7O_5S$ $[M+H]^+$: 576, found 576.
11-3		4-fluorophenyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{28}H_{29}FN_7O_5S$ $[M+H]^+$: 594, found 594.
11-4		neopentyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{27}H_{36}N_7O_5S$ $[M+H]^+$: 570, found 570.

11-5		ethyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{24}H_{30}N_7O_5S$ $[M+H]^+$: 528, found 528.
11-6		isopropyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{25}H_{32}N_7O_5S$ $[M+H]^+$: 542, found 542.

Example 12-1

methyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate



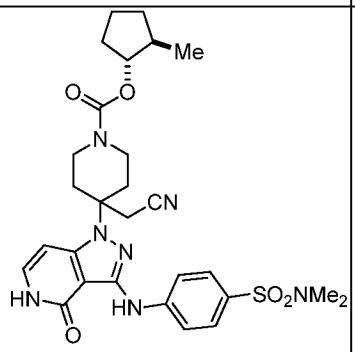
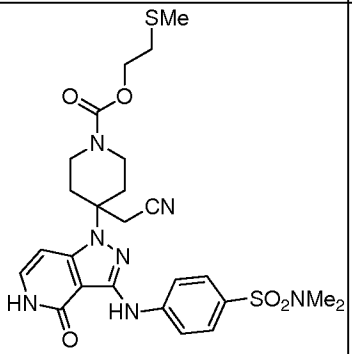
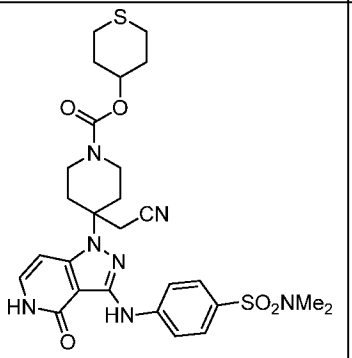
12-1

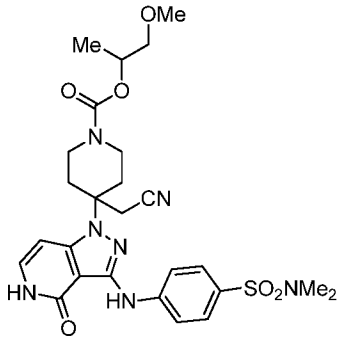
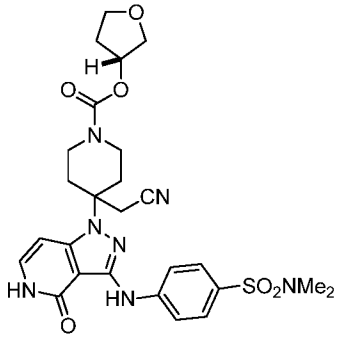
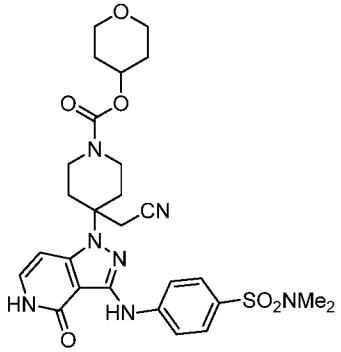
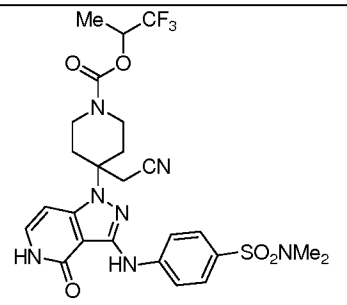
To a DMSO solution (0.5 M) of triethylamine (46 mg, 0.45 mmol) and 2-methoxy ethanol (11 mg, 0.15 mmol) was added *N,N'*-disuccinimidyl carbonate (38 mg, 0.15 mmol). The reaction mixture was stirred at room temperature for 4 hours then a DMSO (0.5 M) solution of 3-((4-(benzyloxy)-1-(4-(cyanomethyl)piperidin-4-yl)-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N,N*-dimethylbenzenesulfonamide (9-1a) (41 mg, 0.075 mmol) was added. The reaction mixture was stirred at room temperature overnight, then quenched by addition of TFA (0.10 mL) and then neutralized after benzyl ether cleavage by addition of PS-Carbonate (300 mg). The reaction was filtered and purified using mass directed reverse phase column chromatography to afford compound 12-1. LRMS (ESI) calc'd for $C_{25}H_{32}N_7O_6S$ [M+H]+: 558, found 558. ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.31 (d, *J* = 5.9 Hz, 1H), 8.71 (s, 1H), 7.85 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* =

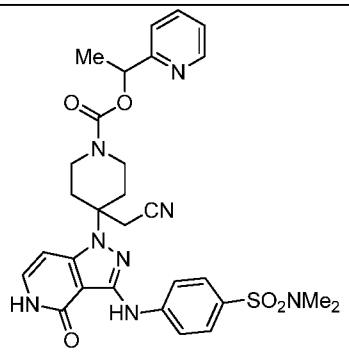
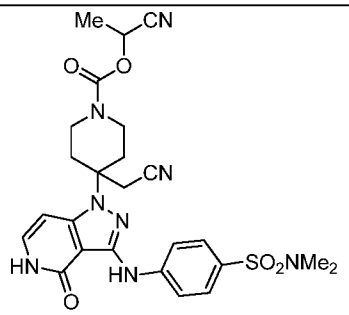
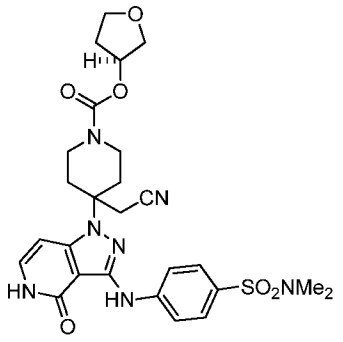
8.6 Hz, 2H), 7.19 (m, 1H), 6.70 (m, 1H), 3.85–3.65 (m, 4H), 3.47–3.37 (m, 4H), 3.32 (s, 3H), 2.72–2.64 (m, 2H), 2.57 (s, 6H), 2.10–2.02 (m, 2H), 1.85–1.75 (m, 2H).

The following compounds in Table 15 were prepared in an analogous manner to that of Example 12-1.

Table 15

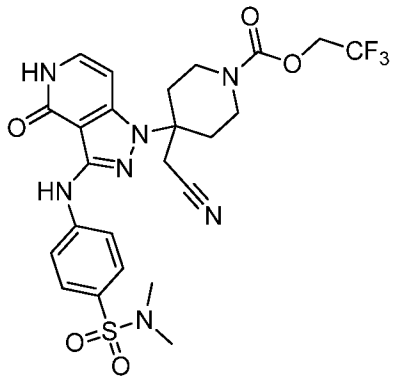
Example	Structure	Compound Name	LRMS
12-2		(*trans* racemic)-2-methylcyclopentyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl) amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{28}H_{36}N_7O_5S$ $[M+H]^+$: 582, found 582.
12-3		2-(methylthio)ethyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl) amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{25}H_{32}N_7O_5S_2$ $[M+H]^+$: 574, found 574.
12-4		tetrahydro-2*H*-thiopyran-4-yl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl) amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{27}H_{34}N_7O_5S_2$ $[M+H]^+$: 600, found 600.

12-5		1-methoxypropan-2-yl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl) amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{26}H_{34}N_7O_6S$ $[M+H]^+$: 572, found 572.
12-6		(*R*)-tetrahydrofuran-3-yl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl) amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{26}H_{32}N_7O_6S$ $[M+H]^+$: 570, found 570.
12-7		tetrahydro-2*H*-pyran-4-yl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl) amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{27}H_{34}N_7O_6S$ $[M+H]^+$: 584, found 584.
12-8		1,1,1-trifluoropropan-2-yl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl) amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{25}H_{29}F_3N_7O_5S$ $[M+H]^+$: 596, found 596.

12-9		1-(pyridin-2-yl)ethyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl) amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{29}H_{33}N_8O_5S$ $[M+H]^+$: 605, found 605.
12-10		1-cyanoethyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl) amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{25}H_{29}N_8O_5S$ $[M+H]^+$: 553, found 553.
12-11		(*S*)-tetrahydrofuran-3-yl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl) amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate	LRMS (ESI) calc'd for $C_{26}H_{32}N_7O_6S$ $[M+H]^+$: 570, found 570.

Example 13

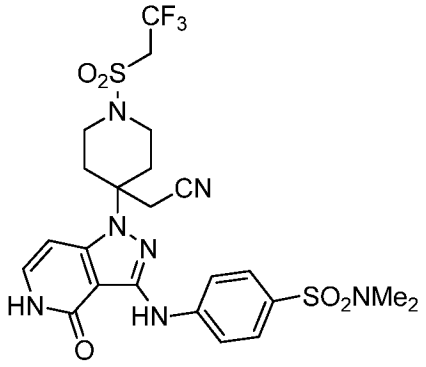
2,2,2-trifluoroethyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate



To a solution of 4-((1-(4-(cyanomethyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethyl benzenesulfonamide (9-1a) (82 mg, 0.25 mmol) in DMF (1.0 mL) was added 2,2,2-trifluoroethanol (50 mg, 0.50 mmol) and Et_3N (50 mg, 0.50 mmol). The solution was cooled to -20°C, then triphosgene (4.0 mg, 1.3 mmol) was added and the resulting solution was stirred at -20°C for 4 hours. The mixture was then filtered, and the filtrate was concentrated *in vacuo* and purified by reverse phase HPLC using water/acetonitrile with 0.225% formic acid modifier to give compound 13 as a white solid. LRMS (ESI) calc'd for $C_{24}H_{27}F_3N_7O_5S$ [M+H]+: 582, found 582. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 11.37 (s, 1H), 8.72 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.66–7.64 (m, 2H), 7.24–7.21 (m, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 4.71–4.69 (m, 2H), 3.86–3.82 (m, 2H), 3.28 (s, 2H), 2.73–2.73 (m, 2H), 2.59 (s, 6H), 2.13–1.97 (m, 4H).

Example 14-1

4-((1-(4-(cyanomethyl)-1-((2,2,2-trifluoroethyl)sulfonyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide

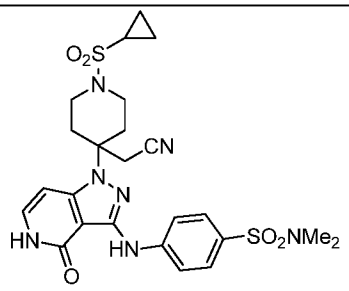


14-1

To a CH_2Cl_2 solution (0.51 mL, 0.1 M) of 2,6-lutidine (28 mg, 0.257 mmol) and 3-((4-(benzyloxy)-1-(4-(cyanomethyl)piperidin-4-yl)-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide (9-1a) (28 mg, 0.051 mmol), 2,2,2-trifluoroethanesulfonyl chloride (12 mg, 0.063 mmol) was added. The reaction mixture was stirred at room temperature for 24 hours followed by the addition of TFA (0.2 mL). The reaction mixture was stirred at room temperature for an additional 4 hours. The reaction was quenched with PS-Carbonate (250 mg), filtered, and purified using mass directed reverse phase column chromatography to afford compound 14-1. LRMS (ESI) calc'd for $C_{23}H_{27}F_3N_7O_5S_2$ [M+H]+: 602, found 602. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 11.31 (d, *J* = 5.9 Hz, 1H), 8.71 (s, 1H), 7.85 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.19 (m, 1H), 6.70 (m, 1H), 4.49–4.41 (m, 2H), 3.75–3.65 (m, 2H), 3.47–3.37 (m, 2H), 3.30–3.23 (m, 2H), 2.89–2.82 (m, 2H), 2.57 (s, 6H), 2.24–2.12 (m, 2H).

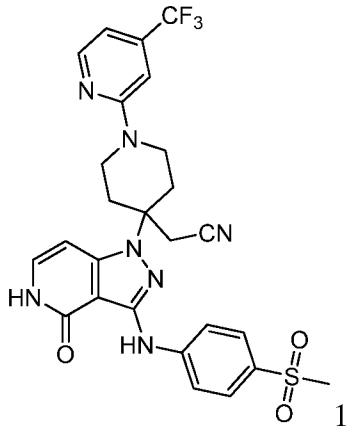
The following compound in Table 16 was prepared in an analogous manner to that of Example 14-1:

Table 16

Example	Structure	Compound Name	LRMS
14-2		4-((1-(4-(cyanomethyl)-1-(cyclopropylsulfonyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{24}H_{30}N_7O_5S_2$ $[M+H]^+$: 560, found 560.

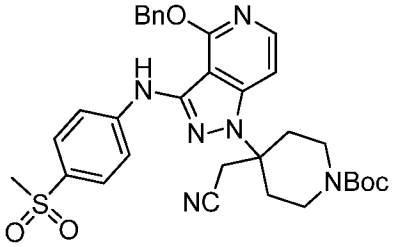
Example 15-1

2-(4-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)acetonitrile



15-1

Step 1: <u>*tert*-butyl 4-(4-(benzyloxy)-3-((4-(methylsulfonyl)phenyl)amino)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate</u>

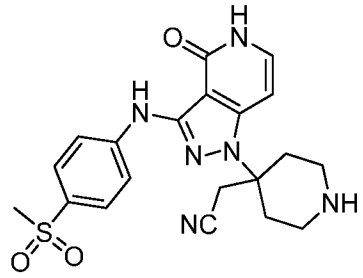


15-1a

To a suspension of *tert*-butyl 4-(3-amino-4-(benzyloxy)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate (0.69 g, 1.5 mmol) and KOAc (200 mg, 2.04 mmol) in *i*-PrOH (4.0 mL) was added 4-bromophenyl methyl sulfone (0.47 g, 2.0 mmol) followed by $Pd_2(dba)_3$ (140 mg, 0.153 mmol) and 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (60 mg, 0.15 mmol) under nitrogen. The resulting suspension was heated to 105 °C by microwave for 1 hour. The mixture was then cooled to room temperature and filtered. The filtrate was purified by preparative TLC, eluting with 50% EtOAc in hexanes, to give compound 15-1a as a white solid. LRMS (ESI) calc'd for $C_{32}H_{37}N_6O_5S$ [M+H]+: 617, found

617. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 6.4 Hz, 1H), 7.86 (d, *J* = 7.2 Hz, 2H), 7.76 (br s, 1 H), 7.56–7.42 (m, 7H), 6.99 (d, *J* = 6.4 Hz, 1H), 5.61 (s, 2H) , 4.10–3.92 (m, 2H), 3.21–3.10 (m, 2H), 3.04 (s, 3H), 2.99–2.95 (m, 2H), 2.92 (s, 2H), 2.14–2.08 (m, 2H), 1.49 (s, 9H).

Step 2: 2-(4-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*] pyridin-1-yl)piperidin-4-yl) acetonitrile (HCl salt)



15-1b

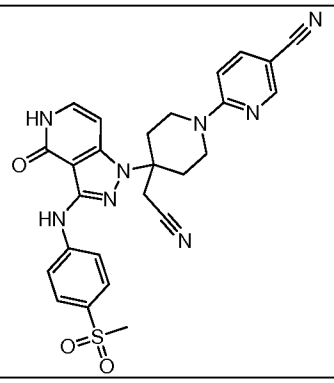
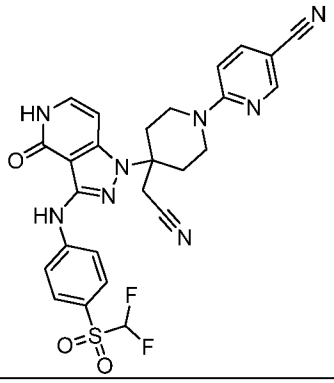
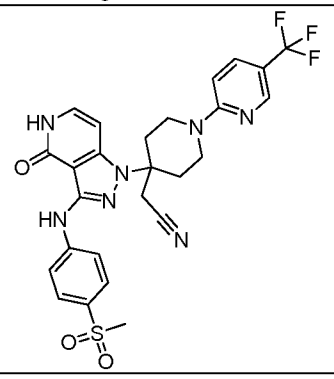
To a suspension of *tert*-butyl 4-(4-(benzyloxy)-3-((4-(methylsulfonyl) phenyl)amino)-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl) piperidine-1-carboxylate (160 mg, 0.260 mmol) in EtOAc (2 mL) was added HCl (2 mL, 4M in EtOAc, 8 mmol). The resulting suspension was stirred for 4 hours at room temperature. The mixture was then filtered, and the solid was washed with EtOAc and dried to afford the desired compound 15-1b HCl salt as a white solid. LRMS (ESI) calc'd for $C_{20}H_{23}N_6O_3S$ [M+H]+: 427, found 427. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 11.46 (d, *J* = 5.6 Hz, 1H), 8.90 (br s, 2H), 8.77 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 4H), 7.80 (d, *J* = 9.2 Hz, 2H), 7.30–7.26 (m, 1H), 6.79 (d, *J* = 7.6 Hz, 2H), 3.34–3.29 (m, 2H), 3.27 (s, 2H), 3.12 (s, 3H), 3.04–2.98 (m, 2H), 2.91–2.88 (m, 2H), 2.30–2.25 (m, 2H).

Step 3: 6-(4-(cyanomethyl)-4-(3-((4-((difluoromethyl)sulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidin-1-yl) nicotinonitrile

To a solution of 2-(4-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidin-4-yl)acetonitrile (0.10 g, 0.24 mmol) in DMF (1.0 mL) was added 2-chloro-4-(trifluoromethyl)pyridine (56 mg, 0.31 mmol) and DIPEA (61 mg, 0.48 mmol). The reaction was sealed and heated to 120 °C for 16 hours, then cooled and filtered and the filtrate was purified by reverse phase HPLC. LRMS (ESI) calc'd for $C_{26}H_{25}N_7O_3SF_3$ [M+H]+: 572, found 572. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 11.41 (br s, 1H), 8.75 (s, H), 8.34 (d, *J* = 4.8 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.28–7.23 (m, 1H), 7.15 (s, 1H), 6.86 (d, *J* = 4.8 Hz), 6.75 (d, *J* = 7.6 Hz, 1H), 4.18–4.09 (m, 2 H), 3.44–3.28 (m, 4H), 3.16 (s, 3H), 2.81–2.72 (m, 2H), 2.18–2.04 (m, 2H).

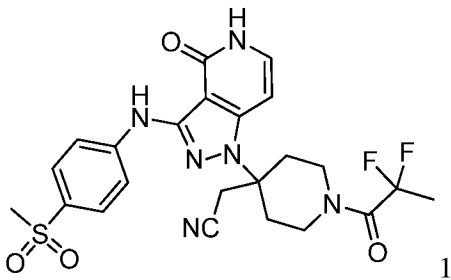
Following analogous procedures outlined for Example 15-1 above, the following compounds in Table 17 were prepared.

Table 17

Example	Structure	Compound Name	LRMS
15-2		6-(4-(cyanomethyl)-4-(3-((4(methylsulfonyl) phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*] pyridin-1-yl)piperidin-1-yl)nicotinonitrile	LRMS (ESI) calc'd for $C_{26}H_{25}N_8O_3S$ $[M+H]^+$: 529, found 529.
15-3		6-(4-(cyanomethyl)-4-(3-((4((difluoromethyl) sulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidin-1-yl)nicotinonitrile	LRMS (ESI) calc'd for $C_{26}H_{23}N_8O_3SF_2$ $[M+H]^+$: 565, found 565.
15-4		2-(4-(3-((4-(methyl sulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1-(5 (trifluoromethyl)pyridin-2-yl)piperidin-4-yl)acetonitrile	LRMS (ESI) calc'd for $C_{26}H_{25}N_7O_3SF_3$ $[M+H]^+$: 572, found 572.

Example 16

2-(1-(2,2-difluoropropanoyl)-4-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidin-4-yl)acetonitrile

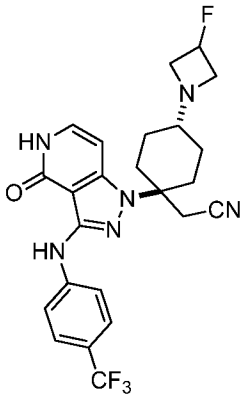


16

To a suspension of 2-(4-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidin-4-yl)acetonitrile (15-1b) (0.10 g, 0.22 mmol) in DMF (2.0 mL) was added HATU (20 mg) and 2,2-difluoropropanoic acid (24 mg, 0.023 mmol). The resulting suspension was stirred for 4 hours at room temperature, then partitioned between water and DCM, and the organic phase was washed with brine and concentrated *in vacuo*. The residue was purified by reverse phase HPLC, eluting with water/acetonitrile with 0.225% formic acid modifier to obtain compound 16. LRMS (ESI) calc'd for $C_{23}H_{24}F_2N_6O_4S$ $[M+H]^+$: 519, found 519. ^1H NMR (400 MHz, DMSO-*d6*): δ 11.40 (d, *J* = 4.4 Hz, 1H), 8.75 (s, 1H), 7.88 (d, *J* = 8.8 Hz, 1H),7.81 (d, *J* = 8.8 Hz, 2H), 7.26–7.22 (m, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 4.13–4.02 (m, 2H), 3.45–3.40 (m, 2H), 3.31 (s, 2H), 3.15 (s, 3H), 2.88–2.77 (m, 2H), 2.16–2.12 (m, 2H), 1.86 (t, *J* = 20 Hz, 3H).

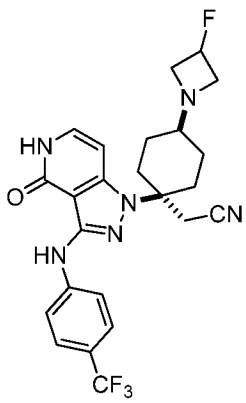
Examples 17-1 and 17-2

(cis and trans) 2-(4-(3-fluoroazetidin-1-yl)-1-(4-oxo-3-((4-(trifluoromethyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile



Diastereomer 1 "trans"

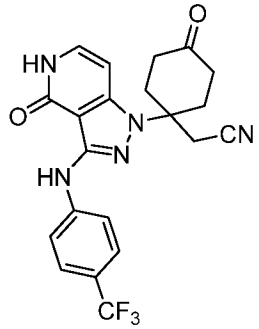
Example 17-1



Diastereomer 2 "cis"

Example 17-2

Step 1: 2-(4-oxo-1-(4-oxo-3-((4-(trifluoromethyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile



17-a

To a suspension of 2-(8-(4-oxo-3-((4-(trifluoromethyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1,4-dioxaspiro[4.5]decan-8-yl)acetonitrile (Example

5-83) (0.30 g, 0.63 mmol) in THF (3.2 mL) was added 2.0 M aqueous HCl (0.64 mL, 1.3 mmol). The reaction mixture was stirred at 75 °C for 2 hours, then the reaction was neutralized with aqueous 2M sodium carbonate. The reaction was then purified by silica chromatography, eluting with 0–6% MeOH in DCM to give compound 17-a. LRMS (ESI) calc'd for $C_{21}H_{19}F_3N_5O_2$ $[M+H]^+$: 430, found 430. ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.34 (d, *J* = 5.6 Hz, 1H), 8.59 (s, 1H), 7.81 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.20 (dd, *J* = 7.4, 5.9 Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 3.30 (s, 2H), 3.00–2.94 (m, 2H), 2.40–2.28 (m, 6H).

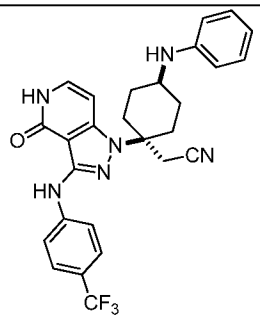
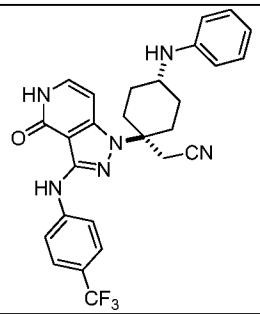
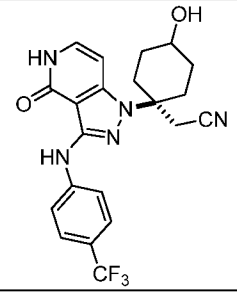
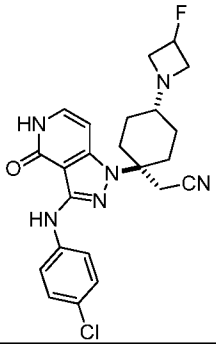
Step 2: (cis and trans) 2-(4-(3-fluoroazetidin-1-yl)-1-(4-oxo-3-((4-(trifluoromethyl)phenyl) amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile

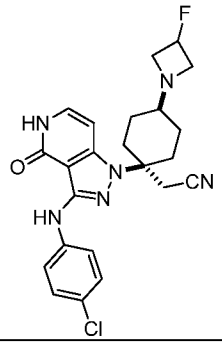
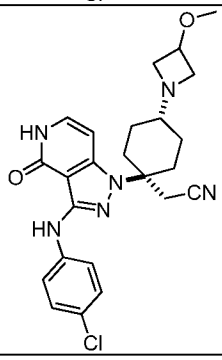
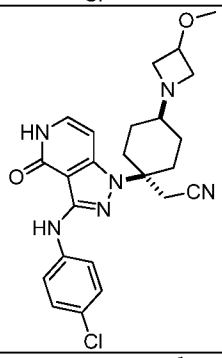
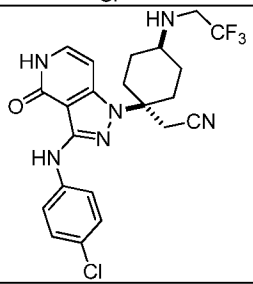
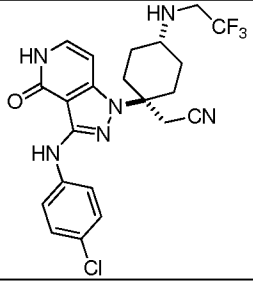
To a suspension of 2-(4-oxo-1-(4-oxo-3-((4-(trifluoromethyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile (0.12 g, 0.27 mmol) in a mixture of THF (1.1 mL) and MeOH (1.1 mL) was added 3-fluoroazetidine hydrochloride (0.75 g, 0.67 mmol) and acetic acid (0.12 mL, 2.1 mmol). The reaction mixture was stirred at room temperature for 15 minutes then sodium cyanoborohydride (0.42 g, 0.67 mmol) was added and the reaction mixture was allowed to stir for an additional 30 minutes at room temperature. The reaction mixture was concentrated *in vacuo* to afford a residue that was purified by silica chromatography, eluting with 0.5–5% MeOH in DCM to give pure trans compound 17-1 (diastereomer 1). LRMS (ESI) calc'd for $C_{24}H_{25}F_4N_6O$ $[M+H]^+$: 489, found 489. ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.27 (d, *J* = 5.6 Hz, 1H), 8.55 (s, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.16–7.13 (m, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 5.20–5.04 (m, 1H), 3.57–3.48 (m, 2H), 3.16 (s, 2H), 3.05–3.01 (m, 1H), 3.01–2.96 (m, 1H), 2.40–2.33 (m, 2H), 2.25–2.21 (m, 1H), 2.13 (t, *J* = 10.0 Hz, 2H), 1.53–1.38 (m, 4H). Cis compound 17-2, (diastereomer 2) was subjected to subsequent purification by reverse phase chromatography using AcCN in water with 0.1% TFA modifier. The desired fractions were diluted with EtOAc and neutralized with saturated aqueous $NaHCO_3$ and the organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. LRMS (ESI) calc'd for $C_{24}H_{25}F_4N_6O$ $[M+H]^+$: 489, found 489. ^{1}H NMR (600 MHz, DMSO-*d6*): δ 11.27 (d, *J* = 5.7 Hz, 1H), 8.56 (s, 1H), 7.80 (d, *J* = 8.6 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.16 (dd, *J* = 7.4, 5.9 Hz, 1H), 6.63 (d, *J* = 7.5 Hz, 1H), 5.10–4.94 (m, 1H), 3.48–3.39 (m, 2H), 3.13 (s, 2H), 3.01–2.91 (m, 2H), 2.73 (d, *J* = 13.7 Hz, 2H), 2.19–2.12 (m, 1H), 1.84–1.72 (m, 2H), 1.68 (dd, *J* = 9.9, 3.9 Hz, 2H), 1.08–0.97 (m, 2H).

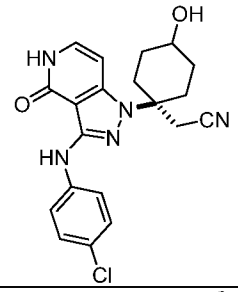
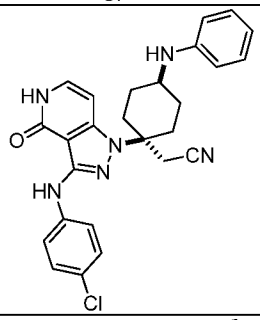
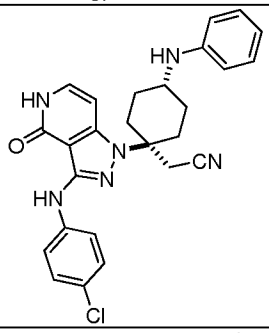
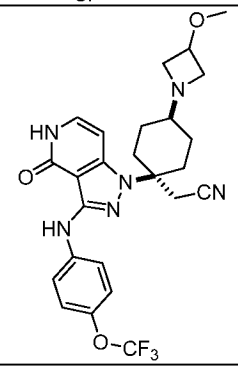
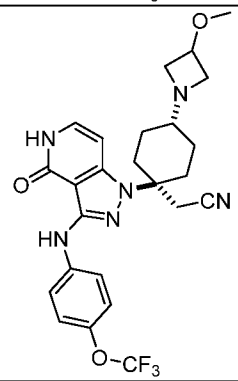
The following examples in Table 18 were prepared in an analogous fashion to that of Examples 17-1 and 17-2 above and relative stereochemistry was assigned by either NMR proof or by analogy based on biochemical activity. In the following examples, cis and trans stereochemistry refers to the relative orientation of the pyrrolopyrimidinone and amine

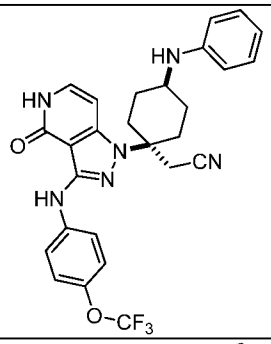
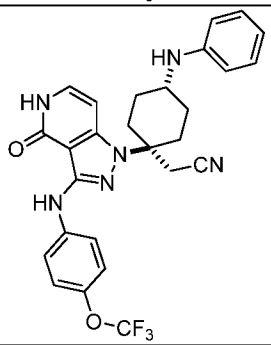
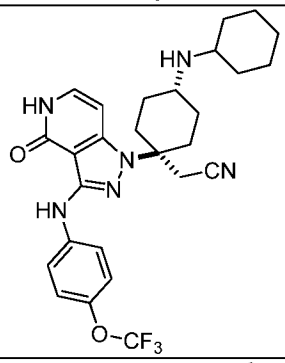
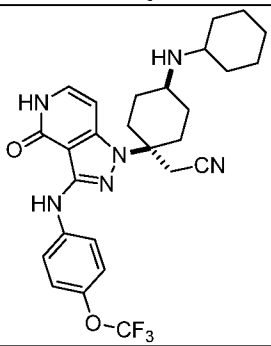
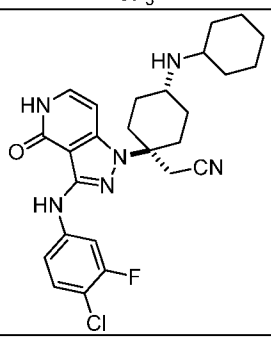
substituents. In some cases, Step 1 of the sequence could be carried out using by substituting *t*-BuXphos ligand, *i*-PrOH and KOAc while using microwave irradiation:

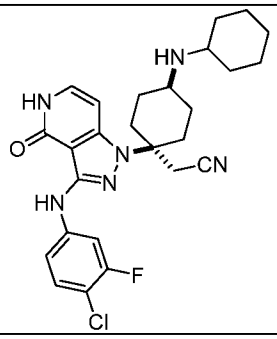
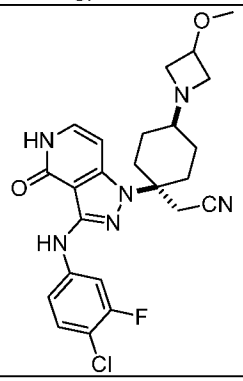
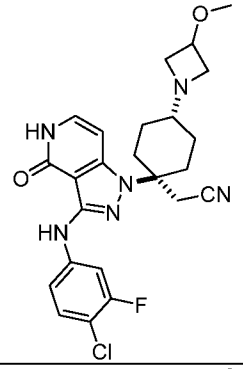
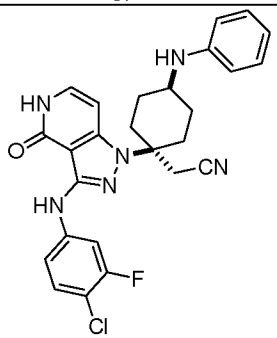
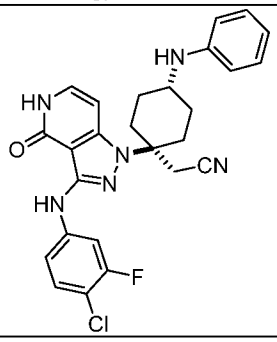
Table 18

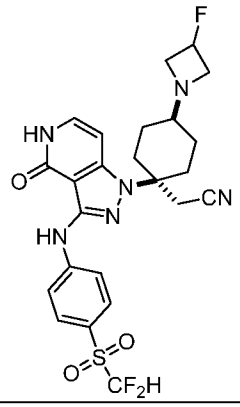
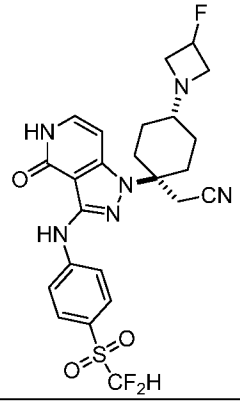
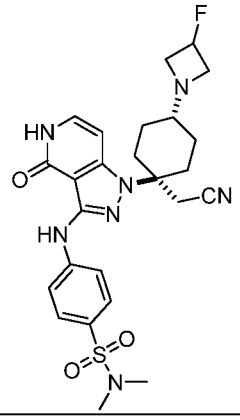
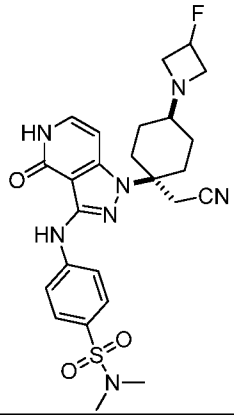
Example	Structure	Compound Name	LRMS
17-3		Cis 2-(1-(4-oxo-3-((4-(trifluoromethyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(phenylamino)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{27}H_{26}F_3N_6O$ $[M+H]^+$: 507, found 507.
17-4		Trans 2-(1-(4-oxo-3-((4-(trifluoromethyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(phenylamino)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{27}H_{26}F_3N_6O$ $[M+H]^+$: 507, found 507.
17-5		(cis and trans) 2-(4-hydroxy-1-(4-oxo-3-((4-(trifluoromethyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{21}H_{21}F_3N_5O_2$ $[M+H]^+$: 432, found 432.
17-6		Trans 2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(3-fluoroazetidin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{23}H_{25}ClFN_6O$ $[M+H]^+$: 455, found 455.

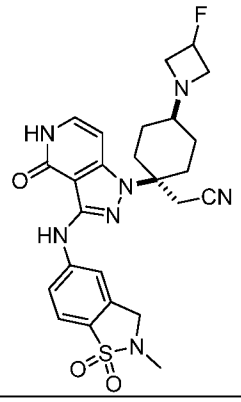
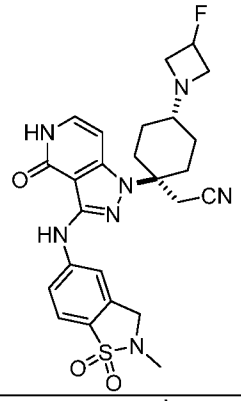
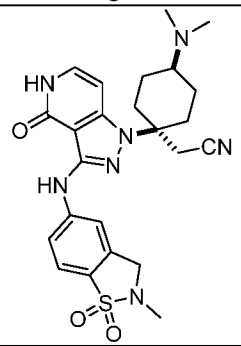
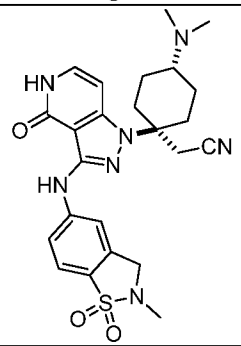
17-7		Cis 2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(3-fluoroazetidin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{23}H_{25}ClFN_6O$ $[M+H]^+$: 455, found 455.
17-8		Trans 2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(3-methoxyazetidin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{24}H_{28}ClN_6O_2$ $[M+H]^+$: 467, found 467.
17-9		Cis 2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(3-methoxyazetidin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{24}H_{28}ClN_6O_2$ $[M+H]^+$: 467, found 467.
17-10		Cis 2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-((2,2,2-trifluoroethyl)amino)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{22}H_{23}ClF_3N_6O$ $[M+H]^+$: 479, found 479.
17-11		Trans 2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-((2,2,2-trifluoroethyl)amino)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{22}H_{23}ClF_3N_6O$ $[M+H]^+$: 479, found 479.

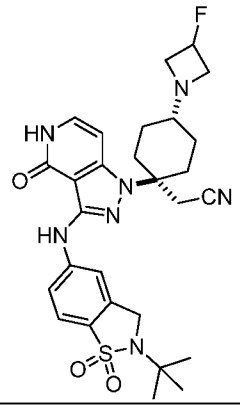
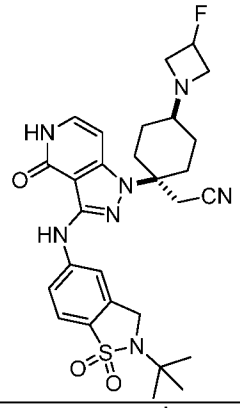
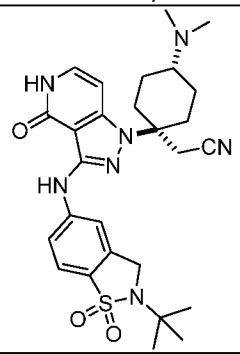
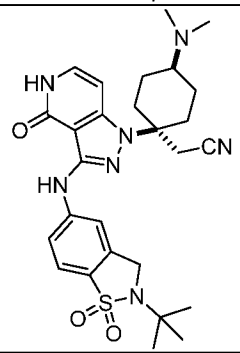
17-12		Cis and trans 2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-hydroxycyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{20}H_{21}ClN_5O_2$ $[M+H]^+$: 398, found 398.
17-13		Cis 2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(phenylamino)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{26}H_{26}ClN_6O$ $[M+H]^+$: 473, found 473.
17-14		Trans 2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(phenylamino)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{26}H_{26}ClN_6O$ $[M+H]^+$: 473, found 473.
17-15		Cis 2-(4-(3-methoxyazetidin-1-yl)-1-(4-oxo-3-((4-(trifluoromethoxy)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{25}H_{28}F_3N_6O_3$ $[M+H]^+$: 517, found 517.
17-16		Trans 2-(4-(3-methoxyazetidin-1-yl)-1-(4-oxo-3-((4-(trifluoromethoxy)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{25}H_{28}F_3N_6O_3$ $[M+H]^+$: 517, found 517.

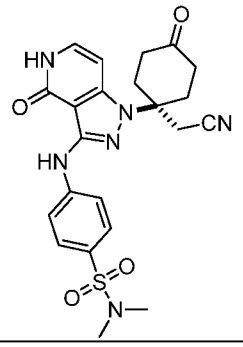
17-17		Cis 2-(1-(4-oxo-3-((4-(trifluoromethoxy)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(phenylamino)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{27}H_{26}F_3N_6O_2$ $[M+H]^+$: 523, found 523.
17-18		Trans 2-(1-(4-oxo-3-((4-(trifluoromethoxy)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(phenylamino)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{27}H_{26}F_3N_6O_2$ $[M+H]^+$: 523, found 523.
17-19		Trans 2-(4-(cyclohexylamino)-1-(4-oxo-3-((4-(trifluoromethoxy)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{27}H_{32}F_3N_6O_2$ $[M+H]^+$: 529, found 529.
17-20		Cis 2-(4-(cyclohexylamino)-1-(4-oxo-3-((4-(trifluoromethoxy)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{27}H_{32}F_3N_6O_2$ $[M+H]^+$: 529, found 529.
17-21		Trans 2-(1-(3-((4-chloro-3-fluorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyclohexylamino)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{26}H_{31}ClFN_6O$ $[M+H]^+$: 497, found 497.

17-22		Cis 2-(1-(3-((4-chloro-3-fluorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyclohexylamino)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{26}H_{31}ClFN_6O$ $[M+H]^+$: 497, found 497.
17-23		Cis 2-(1-(3-((4-chloro-3-fluorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(3-methoxyazetidin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{24}H_{27}ClFN_6O_2$ $[M+H]^+$: 485, found 485.
17-24		Trans 2-(1-(3-((4-chloro-3-fluorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(3-methoxyazetidin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{24}H_{27}ClFN_6O_2$ $[M+H]^+$: 485, found 485.
17-25		Cis 2-(1-(3-((4-chloro-3-fluorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(phenylamino)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{26}H_{25}ClFN_6O$ $[M+H]^+$: 491, found 491.
17-26		Trans 2-(1-(3-((4-chloro-3-fluorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(phenylamino)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{26}H_{25}ClFN_6O$ $[M+H]^+$: 491, found 491.

17-27		Cis 2-(1-(3-((4-((difluoromethyl)sulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(3-fluoroazetidin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{24}H_{26}F_3N_6O_3S$ $[M+H]^+$: 535, found 535.
17-28		Trans 2-(1-(3-((4-((difluoromethyl)sulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(3-fluoroazetidin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{24}H_{26}F_3N_6O_3S$ $[M+H]^+$: 535, found 535.
17-29		Trans 4-((1-(1-(cyanomethyl)-4-(3-fluoroazetidin-1-yl)cyclohexyl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N,N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{25}H_{31}N_7O_3FS$ $[M + H]^+$: 528, found 528.
17-30		Cis 4-((1-(1-(cyanomethyl)-4-(3-fluoroazetidin-1-yl)cyclohexyl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N,N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{25}H_{31}N_7O_3FS$ $[M + H]^+$: 528, found 528.

17-31		Cis 2-(4-(3-Fluoroazetidin-1-yl)-1-(3-((2-methyl-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-6-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{25}H_{29}N_7O_3SF$ $[M + H]^+$: 526, found 526.
17-32		Trans 2-(4-(3-Fluoroazetidin-1-yl)-1-(3-((2-methyl-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-6-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{25}H_{29}N_7O_3SF$ $[M + H]^+$: 526, found 526.
17-33		Cis 2-(4-(Dimethylamino)-1-(3-((2-methyl-1,1-dioxido-2,3-dihydrobenzo-[*d*]isothiazol-6-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{24}H_{30}N_7O_3S$ $[M + H]^+$: 496, found 496.
17-34		Trans 2-(4-(Dimethylamino)-1-(3-((2-methyl-1,1-dioxido-2,3-dihydrobenzo-[*d*]isothiazol-6-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{24}H_{30}N_7O_3S$ $[M + H]^+$: 496, found 496.

17-35		Trans 2-(4-(3-Fluoroazetidin-1-yl)-1-(3-((2-methyl-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-6-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{28}H_{35}N_7O_3SF$ $[M + H]^+$: 568, found 568.
17-36		Cis 2-(4-(3-Fluoroazetidin-1-yl)-1-(3-((2-methyl-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-6-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{28}H_{35}N_7O_3SF$ $[M + H]^+$: 568, found 568.
17-37		Trans 2-(1-(3-((2-(*tert*-Butyl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(dimethylamino)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{27}H_{36}N_7O_3S$ $[M + H]^+$: 538, found 538.
17-38		Cis 2-(1-(3-((2-(*tert*-Butyl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(dimethylamino)cyclohexyl)acetonitrile	LRMS (ESI) calc'd for $C_{27}H_{36}N_7O_3S$ $[M + H]^+$: 538, found 538.

17-39		4-((1-(1-(Cyanomethyl)-4-oxocyclohexyl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide	LRMS (ESI) calc'd for $C_{22}H_{25}N_6O_4S$ $[M + H]^+$: 469, found 469.

BIOLOGICAL ASSAYS

Jak Biochemical HTRF Assay Protocol

The ability of compounds to inhibit the activity of JAK1, JAK2, JAK3, and Tyk2 was measured using a recombinant purified GST-tagged catalytic domain for each enzyme (Invitrogen JAK1 #M4290, JAK2 #M4290, JAK3 #M4290, Tyk2 #M4290) in an HTRF format biochemical assay. The reactions employed a common peptide substrate, LCB-EQEDEPEGDYFEWLW-NH2 (in-house). The basic assay protocol is as follows: First, 250 nL of diluted compounds in DMSO were dispensed into the wells of a dry 384-well Black plate (Greiner #781076) using a Labcyte Echo 555 acoustic dispenser. Subsequent reagent additions employed an Agilent Bravo. Next, 18 μL of 1.11X enzyme and 1.11X substrate in 1X assay buffer (Invitrogen kinase buffer # PV3189, 2 mM DTT, 0.05% BSA) were added to the wells and shaken and then preincubated for 30 minutes at room temperature to allow compound binding to equilibrate. After equilibration, 2 μL of 10X ATP in 1X assay buffer was added to initiate the kinase reaction and the plates were shaken and then incubated at room temperature for 120 minutes. At the end of the incubation, 20 μL of 2X stop buffer (streptavidin-Dylight 650 (Thermo #84547B/100mL), Eu-tagged pY20 antibody (Perkin Elmer #AD0067), EDTA, HEPES, and Triton) was added to quench the reaction. Plates were shaken and centrifuged and then incubated 60 minutes at room temperature and then read on a Perkin Elmer Envision (λ_{ex} = 337 nm, λ_{em} = 665 and 615 nm, TRF delay time = 20 μs). HTRF signal = 10,000 * 665 nm reading / 615 nm reading. After normalization to untreated controls, the percent inhibition of the HTRF signal at each compound concentration was calculated. The plot of percent inhibition versus the log of compound concentration was fit with a 4-parameter dose response equation to calculate IC_{50} values.

Final reaction conditions were:

Enzyme	[E] (nM)	[S] (μM)	[ATP] (μM)	[Eu-pY20] (nM)	[SA-Dylight] (nM)
JAK1	1.405	0.75	31.8	9	312.5

JAK2	0.052	0.75	8.5	9	312.5
JAK3	0.031	0.75	2.9	9	312.5
Tyk2	2.612	0.75	6.9	9	312.5

Compound concentrations tested were 1496, 499, 175, 49.9, 18.7, 6.2, 2.1, 0.75, 0.24, 0.075, and 0.0125 nM, with 1.25% residual DMSO.

BIOLOGICAL DATA

Examples of the instant invention were evaluated in JAK1 and JAK2 *in vitro* binding assays as described above. The following table tabulates the JAK1 IC_{50} values and JAK2 IC_{50} values disclosed for the instant invention.

Example	JAK1 IC_{50} (nM)	JAK2 IC_{50} (nM)
1-1	2.23	24.97
1-2	0.45	11.86
2-1	48.2	60.3
2-2	49.91	39.82
2-3	67.56	>1496
2-4	207.9	>1481
2-5	20.26	490
3	40.76	2.51
4-1	32.90	217.90
4-2	2.47	37.72
4-3	2.64	35.95
5-1	0.22	0.28
5-2	0.21	0.44
5-3	0.43	1.11
5-4	0.12	0.23
5-5	0.28	0.31
5-6	0.11	0.19
5-7	8.23	46.98
5-8	1.96	20.03
5-9	0.10	0.07
5-10	0.23	1.09
5-11	0.20	0.17
5-12	0.12	0.61

Example	JAK1 IC_{50} (nM)	JAK2 IC_{50} (nM)
5-13	0.50	4.86
5-14	1.07	17.68
5-15	0.27	3.45
5-16	0.12	0.35
5-17	0.09	0.08
5-18	0.10	0.12
5-19	0.08	0.08
5-20	0.15	0.12
5-21	0.15	0.14
5-22	0.15	0.19
5-23	0.24	0.34
5-24	0.20	0.25
5-25	0.19	0.30
5-26	0.09	0.10
5-27	0.22	2.81
5-28	0.13	0.29
5-29	13.46	27.69
5-30	12.63	58.01
5-31	0.26	1.64
5-32	0.13	0.87
5-33	0.03	0.23
5-34	4.74	22.56
5-35	3.43	29.31
5-36	0.09	0.34
5-37	1.93	17.08
5-38	0.23	0.49
5-39	0.06	0.43
5-40	2.06	14.58
5-41	0.09	0.11
5-42	1.60	7.21
5-43	0.07	0.14
5-44	0.14	0.37
5-45	0.82	8.55
5-46	3.53	43.53
5-47	7.27	108.00

Example	JAK1 IC_{50} (nM)	JAK2 IC_{50} (nM)
5-48	0.22	2.26
5-49	0.20	0.34
5-50	11.83	34.51
5-51	0.18	0.49
5-52	11.74	30.31
5-53	0.19	0.57
5-54	0.12	1.62
5-55	0.05	0.12
5-56	0.12	0.19
5-57	0.08	0.13
5-58	0.14	0.18
5-59	0.10	0.15
5-60	1.07	0.46
5-61	0.64	12.68
5-62	0.31	0.32
5-63	2.10	0.70
5-64	0.57	0.46
5-65	0.21	3.22
5-66	0.26	0.43
5-67	0.47	0.52
5-68	0.25	0.33
5-69	0.12	0.17
5-70	0.07	0.58
5-71	0.08	0.15
5-72	0.06	0.26
5-73	0.12	0.35
5-74	0.06	0.27
5-75	0.12	0.37
5-76	0.90	7.89
5-77	0.16	0.34
5-78	0.18	2.12
5-79	0.78	1.27
5-80	0.08	1.21
5-81	0.24	3.73
5-82	0.10	0.31

Example	JAK1 IC_{50} (nM)	JAK2 IC_{50} (nM)
5-83	1.97	21.6
6-1	0.15	0.30
6-2	0.88	1.89
6-3	0.25	0.48
6-4	0.15	0.34
6-5	1.20	1.92
6-6	0.43	0.68
6-7	0.22	0.37
6-8	0.42	0.60
6-9	0.65	0.91
7	421.30	>1496
8	0.09	1.90
9-1	0.17	0.38
9-2	0.44	1.16
9-3	2.32	8.62
9-4	6.90	33.07
9-5	0.20	0.54
9-6	1.94	12.45
9-7	0.21	0.63
9-8	0.29	0.52
9-9	0.19	0.28
9-10	0.19	0.29
9-11	0.24	0.28
9-12	0.26	0.99
9-13	0.31	0.75
9-14	0.73	2.84
9-15	0.53	2.84
9-16	1.54	8.34
9-17	1.40	3.26
9-18	3.16	13.96
9-19	1.19	1.98
10-1	0.11	0.48
10-2	0.08	0.31
10-3	0.24	1.63
10-4	0.65	5.17

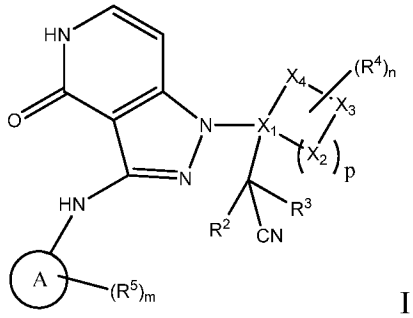
Example	JAK1 IC_{50} (nM)	JAK2 IC_{50} (nM)
10-5	0.55	3.05
10-6	0.08	0.29
10-7	0.09	0.51
10-8	0.16	1.21
10-9	3.96	38.78
10-10	0.17	1.07
10-11	0.14	1.15
10-12	1.69	16.75
10-13	1.08	11.97
10-14	0.23	1.96
10-15	0.81	8.38
10-16	1.05	6.75
10-17	0.15	0.70
10-18	0.14	0.39
10-19	0.26	3.14
10-20	0.31	2.48
10-21	0.08	0.33
10-22	0.09	0.21
10-23	0.14	1.32
10-24	0.14	0.36
10-25	0.10	0.16
11-1	0.13	0.26
11-2	0.19	0.86
11-3	0.27	0.97
11-4	0.45	3.08
11-5	0.12	0.29
11-6	0.12	0.27
12-1	0.27	1.01
12-2	0.38	1.69
12-3	0.31	1.09
12-4	0.27	1.45
12-5	0.27	0.61
12-6	0.12	0.47
12-7	0.18	1.35
12-8	0.18	0.29

Example	JAK1 IC_{50} (nM)	JAK2 IC_{50} (nM)
12-9	0.41	1.37
12-10	0.06	0.10
12-11	0.16	0.91
13	0.11	0.24
14-1	0.09	0.18
14-2	0.06	0.12
15-1	0.16	0.37
15-2	0.04	0.04
15-3	0.25	0.26
15-4	0.20	0.55
16	0.10	0.24
17-1	0.26	0.94
17-2	6.80	64
17-3	41.14	1292
17-4	6.33	101.90
17-5	4.14	84.56
17-6	0.09	1.75
17-7	2.98	19.82
17-8	0.03	2.53
17-9	1.14	102.10
17-10	73.97	1020
17-11	0.22	2.20
17-12	5.41	38.48
17-13	64.96	>1496
17-14	1.71	32.35
17-15	151.20	1137
17-16	0.15	1.43
17-17	119.90	1099
17-18	7.27	54.70
17-19	0.37	36.64
17-20	52.18	>1496
17-21	0.12	64.17
17-22	20.51	>1496
17-23	124.8	>1496
17-24	0.09	5.87

Example	JAK1 IC_{50} (nM)	JAK2 IC_{50} (nM)
17-25	70.15	>1496
17-26	2.48	54.73
17-27	2.23	9.07
17-28	0.05	0.11
17-29	0.10	0.13
17-30	2.62	3.54
17-31	1.81	16.95
17-32	0.04	0.09
17-33	48.51	591.8
17-34	1.07	12.09
17-35	0.21	0.21
17-36	0.83	6.85
17-37	0.23	4.43
17-38	16.14	211.1
17-39	1.37	1.78

CLAIMS

1. A compound of formula I or a pharmaceutically acceptable salt, or a stereoisimer thereof:



I

A is selected from aryl, heteroaryl, cycloalkyl$C_{(0-10)}$alkyl and C_{1-6}alkyl;

R^2 and R^3 are each independently selected from hydrogen, C_{1-4}alkyl and hydroxyl, wherein R^2 and R^3 may optionally, join together with the carbon they are attached to to form a 3 to 6 membered ring;

X_1, X_2, X_3, and X_4 are each independently selected from O, N, S, and C and provided that the formed ring system contains 0, 1, 2, or 3 atoms selected from O, N and S;

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

m is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3, or 4;

R^4 is selected from:

halogen,

oxo (=O),

C_{1-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{1-10} heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{2-10} alkenyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

aryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{3-8} cycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

(C_{3-8})heterocycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,

C_{0-10} alkylamino(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

(C_{1-10})heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10}alkyl,

(C_{1-10})heteroalkylamino(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$alkyl,

C_{3-8} cycloalkyl C_{0-10} alkylaminoC_{0-10} alkyl,

aryl C_{0-10} alkylaminoC_{0-10} alkyl,

heteroaryl C_{0-10} alkylaminoC_{0-10} alkyl,

(C_{3-8})heterocycloalkyl C_{0-10} alkylaminoC_{0-10} alkyl,

C_{1-10} alkylsulfonyl,

C_{1-10} heteroalkylsulfonyl,

(C_{3-8})cycloalkylC_{0-10}alkylsulfonyl,

(C_{3-8})cycloheteroalkylC_{0-10}alkylsulfonyl,

heteroarylC_{0-10} alkylsulfonyl,

arylC_{0-10} alkylsulfonyl,

$-SO_2NH_2$,

$-SO_2NH(C_{1-6}alkyl)$,

$-SO_2N(C_{1-6}alkyl)_2$,

C_{0-10} alkylsulfamoyl,

C_{1-10} heteroalkylsulfamoyl,

(C_{3-8})cycloalkylC_{0-10} alkylsulfamoyl,

(C_{3-8})cycloheteroalkylC_{0-10} alkylsulfamoyl,

heteroarylC_{0-10} alkylsulfamoyl,

arylC_{0-10} alkylsulfamoyl,

$(C_{0-10}$ alkyl$)_{1-2}$ amino,

$-CO_2(C_{0-10}$ alkyl),

$-(C_{0-10}$ alkyl)CO_2H,

$-SO_2CF_3$,

$-SO_2CF_2H$,

C_{1-10} alkylsulfinyl,

C_{1-4}acylamino C_{0-10} alkyl,

hydroxy,

$-(C_{1-10}$ alkyl)OH,

C_{0-10} alkylalkoxy,

cyano,

(C_{1-6}alkyl)cyano, and

C_{1-6}haloalkyl,

wherein two R^4 together with the atoms to which they are attached may optionally form a ring;

R^5 is selected from:

halogen,

oxo (=O),

C_{1-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{1-10} heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{2-10} alkenyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

aryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{3-8} cycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

(C_{3-8})heterocycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,

(C_{1-10})heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,

C_{3-8} cycloalkyl C_{0-10} alkylaminoC_{0-10} alkyl,

aryl C_{0-10} alkylaminoC_{0-10} alkyl,

heteroaryl C_{0-10} alkylaminoC_{0-10} alkyl,

(C_{3-8})heterocycloalkyl C_{0-10} alkylaminoC_{0-10} alkyl,

$-SF_5$,

C_{1-10} alkylsulfonyl,

C_{1-10} heteroalkylsulfonyl,

(C_{3-8})cycloalkylC_{0-10}alkylsulfonyl,

(C_{3-8})cycloheteroalkylC_{0-10}alkylsulfonyl,

heteroarylC_{0-10} alkylsulfonyl,

arylC_{0-10} alkylsulfonyl,

C_{0-10} alkylsulfamoyl,

C_{1-10} heteroalkylsulfamoyl,

(C_{3-8})cycloalkylC_{0-10} alkylsulfamoyl,

(C_{3-8})cycloheteroalkylC_{0-10} alkylsulfamoyl,

heteroarylC_{0-10} alkylsulfamoyl,

$-SO_2NH_2$,

$-SO_2NH(C_{1-6}alkyl)$,

$-SO_2N(C_{1-6}alkyl)_2$,

arylC_{0-10} alkylsulfamoyl,

$(C_{0-10}$ alkyl$)_{1-2}$ amino,

$-CO_2(C_{0-10}$ alkyl),

$-(C_{0-10}$ alkyl$)CO_2H$,

$-SO_2CF_3$,

$-SO_2CF_2H$,

C_{1-10} alkylsulfinyl,

C_{1-4}acylamino C_{0-10} alkyl,

hydroxy,

$-(C_{1-10}$ alkyl$)OH$,

C_{0-10} alkylalkoxy,

cyano,

$(C_{1-6}$alkyl)cyano, and

C_{1-6}haloalkyl; and

wherein R^4 and R^5 are each optionally substituted with 1, 2, 3, or 4 R^6 substituents and R^6 is independently selected from:

halogen,

C_{1-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{1-10} heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{2-10} alkenyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

aryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{3-8} cycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

(C_{3-8})heterocycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

C_{1-10} alkyl(carbonyl)$_{0-1}$oxyC_{0-10} alkyl,

C_{2-10} alkenyl(carbonyl)$_{0-1}$oxyC_{0-10} alkyl,

C_{1-10} heteroalkyl(carbonyl)$_{0-1}$oxyC_{0-10} alkyl,

aryl C_{0-10} alkyl (carbonyl)$_{0-1}$oxyC_{0-10} alkyl,

(C_{3-8})cycloalkyl C_{0-10} alkyl(carbonyl)$_{0-1}$oxyC_{0-10} alkyl,

heteroarylC_{0-10} alkyl(carbonyl)$_{0-1}$oxyC_{0-10} alkyl,

(C_{3-8})heterocycloalkyl C_{0-10} alkyl(carbonyl)$_{0-1}$oxyC_{0-10} alkyl,

((C_{0-10})alkyl)$_{1-2}$aminocarbonyloxy,

aryl (C_{0-10})alkylaminocarbonyloxy,

-CO_2(C_{0-10} alkyl),

-(C_{0-10} alkyl)CO_2H,

oxo (=O),

C_{1-10} alkylsulfonyl,

C_{1-10} heteroalkylsulfonyl,

(C_{3-8}) cycloalkylsulfonyl,

(C_{3-8}) cycloheteroalkylsulfonyl,

heteroarylsulfonyl,

arylsulfonyl,

aminosulfonyl,

-SO_2NH_2,

-SO_2NH(C_{1-6}alkyl),

-SO_2N(C_{1-6}alkyl)$_2$,

-SO_2CF_3,

-SO_2CF_2H,

C_{1-10} alkylsulfinyl,

amino,

(C_{0-10} alkyl)$_{1-2}$ amino,

-(oxy)$_{0-1}$(carbonyl)$_{0-1}$N(C_{0-10} alkyl)$_{1-2}$

C_{1-4}acylamino C_{0-10} alkyl,

hydroxy,

(C_{1-10} alkyl)OH,

C_{1-10} alkoxy,

(C_{1-10} alkyl)cyano,

cyano, and

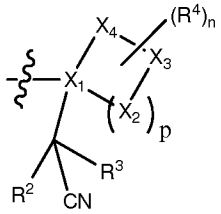
C_{1-6}haloalkyl; and

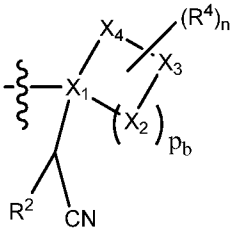
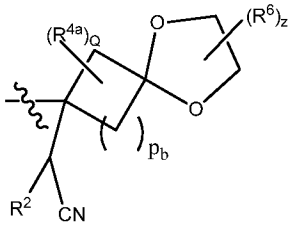
R^6 is optionally substituted with 1, 2, or 3 substituents selected from hydrogen, hydroxy, (C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{1-10} alkyl)OH, halogen, CO_2H, -(C_{0-6})alkylCN, -O(C=O)C_1-C_6 alkyl, NO_2, trifluoromethoxy, trifluoroethoxy, trifluoromethyl, trifluoroethyl, -N-C(O)O(C_{0-6})alkyl, C_{1-10} alkylsulfonyl, oxo (O=), aminosulfonyl, -SO_2C_{1-6}alkyl, -SO_2NH_2, -$SO_2NH(C_{1-6}alkyl)$,-$SO_2N(C_{1-6}alkyl)_2$, -SO_2CF_3, -SO_2CF_2H, -C_{1-10} alkylsulfinyl, -$O_{(0-1)}(C_{1-10})$haloalkyl, amino(C_{1-6}alkyl)$_{0-2}$ and NH_2.

2. A compound according to claim 1, wherein R^5 is selected from: halogen, oxo (=O), C_{1-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{1-10} heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{2-10} alkenyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, aryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{3-8} cycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, (C_{3-8})heterocycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC$_{0-10}$ alkyl, (C_{1-10})heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC$_{0-10}$ alkyl, -SF_5, C_{1-10} alkylsulfonyl, C_{1-10} heteroalkylsulfonyl, (C_{3-8})cycloalkylC$_{0-10}$alkylsulfonyl, (C_{3-8})cycloheteroalkylC$_{0-10}$alkylsulfonyl, heteroarylC$_{0-10}$ alkylsulfonyl, arylC$_{0-10}$ alkylsulfonyl, C_{0-10} alkylsulfamoyl, C_{1-10} heteroalkylsulfamoyl, (C_{3-8})cycloalkylC$_{0-10}$ alkylsulfamoyl, (C_{3-8})cycloheteroalkylC$_{0-10}$ alkylsulfamoyl, heteroarylC$_{0-10}$ alkylsulfamoyl, arylC$_{0-10}$ alkylsulfamoyl, (C_{0-10} alkyl)$_{1-2}$ amino, -CO_2(C_{0-10} alkyl), -(C_{0-10} alkyl)CO_2,-SO_2NH_2, -$SO_2NH(C_{1-6}alkyl)$, -$SO_2N(C_{1-6}alkyl)_2$, H, -SO_2CF_3, -SO_2CF_2H, hydroxy, -(C_{1-10} alkyl)OH, C_{0-10} alkylalkoxy, cyano, (C_{1-6}alkyl)cyano, and C_{1-6}haloalkyl; and wherein R^5 is optionally substituted with 0, 1, 2, 3, or 4 R^6substituents.

3. A compound according to claim 2, wherein R^4 is selected from: halogen, oxo (=O), C_{1-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{1-10} heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, aryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{3-8}cycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,
(C_{3-8})heterocycloalkylC$_{0-10}$ alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{3-8} cycloalkyl C_{0-10} alkylaminoC$_{0-10}$ alkyl, aryl C_{0-10} alkylaminoC$_{0-10}$ alkyl, heteroaryl C_{0-10} alkylaminoC$_{0-10}$

alkyl, (C_{3-8})heterocycloalkyl C_{0-10} alkylaminoC_{0-10} alkyl, C_{1-10} alkylsulfonyl, C_{1-10} heteroalkylsulfonyl, (C_{3-8})cycloalkylC_{0-10}alkylsulfonyl, (C_{3-8})cycloheteroalkylC_{0-10}alkylsulfonyl, heteroarylC_{0-10} alkylsulfonyl, arylC_{0-10} alkylsulfonyl, $-SO_2NH_2$, $-SO_2NH(C_{1-6}alkyl)$, $-SO_2N(C_{1-6}alkyl)_2$, C_{0-10} alkylsulfamoyl, C_{1-10} heteroalkylsulfamoyl, (C_{3-8})cycloalkylC_{0-10} alkylsulfamoyl, (C_{3-8})cycloheteroalkylC_{0-10} alkylsulfamoyl, heteroarylC_{0-10} alkylsulfamoyl, arylC_{0-10} alkylsulfamoyl, (C_{0-10} alkyl)$_{1-2}$ amino, $-CO_2(C_{0-10}$ alkyl), $-(C_{0-10}$ alkyl)CO_2H, hydroxy, $-(C_{1-10}$ alkyl)OH, C_{0-10} alkylalkoxy, and C_{1-6}haloalkyl; wherein R^4 is optionally substituted with 1, 2, 3, or 4 R^6 substituents and two R^4 together with the ring atoms to which they are attached may optionally join together to form a ring.

4. A compound according to claim 4, wherein  is selected from:

 and  ;

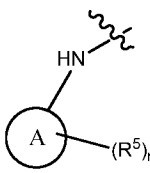
R^2 is hydrogen;

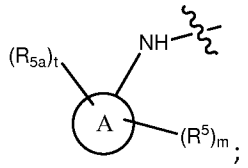
Q is 0, 1, 2 or 3;

R^{4a} is OH, $C_{(1-4)}$alkyl, oxo, or halogen;

p_b is independently 0, 1, 2, 3, or 4; and

Z is 0, 1, or 2, provided that the sum of Q and Z is less than or equal to 4.

5. A compound according to Claim 4, wherein  is selected from:



t is 0, 1, 2 or 3;

m is 0, 1, or 2; and

R^{5a} is selected from halogen, methyl, ethyl, oxo, C_{1-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{1-10} heteroalkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, aryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, C_{3-8} cycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl, and (C_{3-8})heterocycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl;

provided that the sum of t plus m is less than or equal to 4.

6. A compound according to Claim 5, wherein R^{5a} is selected from halogen, methyl, ethyl, oxo, and heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl.

7. A compound of claim 1 or a pharmaceutically acceptable salt, or a stereoisomer thereof selected from:

tert-butyl 3-(cyanomethyl)-3-(4-oxo-3-(phenylamino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)azetidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(4-oxo-3-(phenylamino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-[3-(ethylamino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-{3-[(cyclopropylmethyl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-[3-(cyclobutylamino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate;

tert-butyl 3-(cyanomethyl)-3-[3-(ethylamino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]azetidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-[3-(methylamino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate;

tert-butyl 3-(cyanomethyl)-3-[3-(cyclopropylamino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]azetidine-1-carboxylate;

tert-butyl 3-(cyanomethyl)-3-(4-oxo-3-((2-(trifluoromethyl)pyridin-4-yl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)azetidine-1-carboxylate;

tert-butyl 3-(cyanomethyl)-3-(3((4(methoxycarbonyl)phenyl) amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)azetidine-1-carboxylate;

tert-butyl 3-(cyanomethyl)-3-(3-((4-fluorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)azetidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-[4-oxo-3-({4-[2,2,2-trifluoro-hydroxyethyl]phenyl}amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-{4-oxo-3-[(4-sulfamoylphenyl)amino]-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(4-oxo-3-{[1-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-isoindol-5-yl]amino}-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-3-fluoro-4-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-{3-[(2-methyl-1,1-dioxido-2,3-dihydro-1,2-benzisothiazol-5-yl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(4-oxo-3-{[4-(pentafluorosulfanyl)phenyl]amino}-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(4-oxo-3-{[4-(trifluoromethyl)phenyl]amino}-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-3-fluoro-4-{3-[(2-methyl-1,1-dioxido-2,3-dihydro-1,2-benzisothiazol-5-yl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-3-methyl-4-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(4-oxo-3-((1-oxo-2,3-dihydro-1*H*-inden-5-yl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-{[3-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-3-fluoro-4-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-{[4-(dimethylsulfamoyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-3-fluoro-4-[4-oxo-3-(phenylamino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-3-fluoro-4-[4-oxo-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-4,5-dihydro-*1H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate;

tert-butyl 4-{3-[(2-*tert*-butyl-1,1-dioxido-2,3-dihydro-1,2-benzisothiazol-5-yl)amino]-4-oxo-4,5-dihydro-*1H*-pyrazolo[4,3-*c*]pyridin-1-yl}-4-(cyanomethyl)-3-fluoropiperidine-1-carboxylate;

tert-butyl 4-{3-[(2-*tert*-butyl-1,1-dioxido-2,3-dihydro-1,2-benzisothiazol-5-yl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}-4-(cyanomethyl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-{[1,1-dioxido-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1,2-benzisothiazol-5-yl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-3-fluoropiperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((1,1-dioxido-2-(2,2,2-trifluoroethyl)-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

2-(4-(3-((2-(*tert*-butyl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1-(2,2-difluoropropanoyl)piperidin-4-yl)acetonitrile;

2-(3-(4-oxo-3-(phenylamino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-3-yl)acetonitrile;

4-((1-(3-(cyanomethyl)tetrahydro-2*H*-pyran-3-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide;

2-(3-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-3-yl)acetonitrile;

methyl 5-(cyanomethyl)-5-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate;

tert-butyl 5-(cyanomethyl)-5-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate;

tert-butyl 5-(3-((2-(*tert*-butyl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-5-(cyanomethyl)tetrahydro-2*H*-pyran-2-carboxylate;

tert-butyl 5-(cyanomethyl)-5-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate;

tert-butyl 5-(cyanomethyl)-5-(3-((1,1-dioxido-2-(2,2,2-trifluoroethyl)-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate;

tert-butyl 3-(cyanomethyl)-3-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)azetidine-1-carboxylate;

tert-butyl 3-(cyanomethyl)-3-{3-[(2-fluoropyridin-4-yl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}azetidine-1-carboxylate;

tert-butyl 3-(cyanomethyl)-3-[4-oxo-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]azetidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-{3-[(4-fluorophenyl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)-3-methylphenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 5-(3-((4-1-amino-2,2,2-trifluoroethyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-5-(cyanomethyl)tetrahydro-2*H*-pyran-2-carboxylate;

tert-butyl 5-(cyanomethyl)-5-(4-oxo-3-(phenylamino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate;

tert-butyl 5-(cyanomethyl)-5-(3-((2-methyl-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)tetrahydro-2*H*-pyran-2-carboxylate;

N-(*tert*-butyl)-4-((1-(4-(cyanomethyl)-1-(2,2-difluoropropanoyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)benzenesulfonamide;

2-(1-(2,2-difluoropropanoyl)-4-(3-((4-(isopropylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidin-4-yl)acetonitrile;

N-(*tert*-butyl)-4-((1-(4-(cyanomethyl)-1-(2,2-difluoropropanoyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*-methylbenzenesulfonamide;

2-(4-(3-((4-(*tert*-butylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1-(2,2-difluoropropanoyl)piperidin-4-yl)acetonitrile;

tert-butyl 4-(3-(3,5-bis((1*H*-pyrazol-1-yl)methyl)phenylamino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-(3,5-dimethylphenylamino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(3-(3,5-bis((1*H*-1,2,3-triazol-1-yl)methyl)phenylamino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate;

tert-butyl 4-(3-(3,5-bis((2*H*-1,2,3-triazol-2-yl)methyl)phenylamino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate;

tert-butyl 4-(3-(3-((1*H*-1,2,3-triazol-1-yl)methyl)-5-((2*H*-1,2,3-triazol-2-yl)methyl) phenylamino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate;

tert-butyl 4-(3-(*m*-toluidino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-(isoindolin-5-ylamino)-4-oxo-4,5-dihydropyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl]amino}-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-{[2-(cyclopropylmethyl)-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl]amino}-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-{3-[(2-ethyl-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl)amino]-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate;

methyl 4-(cyanomethyl)-4-[3-[(2-methyl-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl)amino]-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate;

methyl 4-{3-[(2-*tert*-butyl-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl)amino]-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl}-4-(cyanomethyl)piperidine-1-carboxylate;

methyl 4-{3-[(2-ethyl-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl)amino]-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl}-4-(cyanomethyl)piperidine-1-carboxylate;

methyl 4-(cyanomethyl)-4-(3-{[2-(2-methylpropyl)-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl]amino}-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

methyl 4-(cyanomethyl)-4-(3-{[2-(cyclopropylmethyl)-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl]amino}-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

methyl 4-(cyanomethyl)-4-(3-{[2-(cyclopentylmethyl)-1,1-dioxo-2,3-dihydro-1,2-benzothiazol-5-yl]amino}-4-oxo-1*H*,4*H*,5*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-[4-oxo-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl]piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-{[4-(methylsulfonyl)phenyl]amino}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-{3-[(2-fluoropyridin-4-yl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidine-1-carboxylate;

4-(1-(1-(cyanomethyl)cyclohexyl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-ylamino)-*N*,*N*-dimethylbenzenesulfonamide;

2-(1-(3-((2-(*tert*-butyl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile;

2-(1-(3-((2-methyl-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile;

tert-butyl 4-(cyanomethyl)-4-(3-((1,1-dioxido-2,3-dihydrobenzo[*b*]thiophen-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

2-(8-(4-oxo-3-((4-(trifluoromethyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1,4-dioxaspiro[4.5]decan-8-yl)acetonitrile;

tert-butyl 4-(cyanomethyl)-4-(4-oxo-3-((4-(((2,2,2-trifluoroethyl)amino)methyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((4-(*N*-isopropylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(3-((4-(*N*-benzylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((4-(*N*-(cyclopropylmethyl) sulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((4-(*N*-(2-methoxyethyl) sulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((4-(*N*-cyclohexylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(4-oxo-3-((4-(piperidin-1-ylsulfonyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((4-(morpholinosulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((3-fluoro-4-(*N*-isopropylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tert-butyl 4-(cyanomethyl)-4-(3-((4-(*N*-(cyclopropylmethyl)sulfamoyl)-3-fluorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

(4-{3-[(4-fluorophenyl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidin-4-yl)acetonitrile;

[1-(cyclopropylcarbonyl)-4-{3-[(4-fluorophenyl)amino]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl}piperidin-4-yl]acetonitrile;

4-({1-[1-benzyl-4-(cyanomethyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(4-methylbenzyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{4-(cyanomethyl)-1-[4-(trifluoromethyl)benzyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{4-(cyanomethyl)-1-[4-(1-methylethyl)benzyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{4-(cyanomethyl)-1-[4-(1-methylethyl)benzyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzene sulfonamide;

4-[(1-{4-(cyanomethyl)-1-[4-(1methylethoxy)benzyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzene sulfonamide;

4-({1-[4-(cyanomethyl)-1-(4-fluorobenzyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(3-fluorobenzyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzene sulfonamide;

4-({1-[4-(cyanomethyl)-1-(2-fluorobenzyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(2,6-difluorobenzyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzene sulfonamide;

4-({1-[4-(cyanomethyl)-1-(2,3,6-trifluorobenzyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(1,3-oxazol-2-ylmethyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(4-isoxazol-3-ylbenzyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{4-(cyanomethyl)-1-[4-(2-oxopyrrolidin-1-yl)benzyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(3-phenylpropyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzene sulfonamide;

4-({1-[4-(cyanomethyl)-1-(1*H*-indol-4-ylmethyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-((1-(4-(cyanomethyl)-1-(1-(2,6-difluorophenyl)ethyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-((1-(4-(cyanomethyl)-1-phenethylpiperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide;

3-({1-[4-(cyanomethyl)-1-(pyridin-3-ylmethyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-propanoylpiperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(3,3,3-trifluoropropanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(methoxyacetyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(*N*,*N*-dimethylglycyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(cyclopropylcarbonyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{4-(cyanomethyl)-1-[(3,3-difluorocyclobutyl)carbonyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(cyclohexylcarbonyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{4-(cyanomethyl)-1-[tricyclo[3.3.1.13,7]dec-1-ylcarbonyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(cyclopropylacetyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(3-cyclopropylpropanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(phenylcarbonyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{1-[(4-chlorophenyl)carbonyl]-4-(cyanomethyl)piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{1-[(3-chlorophenyl)carbonyl]-4-(cyanomethyl)piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{1-[(2-chlorophenyl)carbonyl]-4-(cyanomethyl)piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-{[4-(trifluoromethyl)phenyl]acetyl}piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(3-phenylpropanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(2,3-dihydro-1*H*-inden-2-ylcarbonyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-[(1-{4-(cyanomethyl)-1-[(2-oxopyrrolidin-1-yl)acetyl]piperidin-4-yl}-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino]-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(tetrahydro-2*H*-pyran-4-ylcarbonyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(4,4,4-trifluorobutanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(3-cyanopropanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-({1-[4-(cyanomethyl)-1-(3,3-dimethylbutanoyl)piperidin-4-yl]-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl}amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-((1-(4-(cyanomethyl)-1-(2-(methylthio)propanoyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-((1-(1-(2-cyanoacetyl)-4-(cyanomethyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide;

methyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

phenyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

4-fluorophenyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

neopentyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

ethyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

isopropyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

methyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

2-methylcyclopentyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

2-(methylthio)ethyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tetrahydro-2*H*-thiopyran-4-yl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

1-methoxypropan-2-yl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tetrahydrofuran-3-yl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tetrahydro-2*H*-pyran-4-yl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

1,1,1-trifluoropropan-2-yl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

1-(pyridin-2-yl)ethyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

1-cyanoethyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

tetrahydrofuran-3-yl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

2,2,2-trifluoroethyl 4-(cyanomethyl)-4-(3-((4-(*N*,*N*-dimethylsulfamoyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidine-1-carboxylate;

4-((1-(4-(cyanomethyl)-1-((2,2,2-trifluoroethyl)sulfonyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide;

4-((1-(4-(cyanomethyl)-1-(cyclopropylsulfonyl)piperidin-4-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N*,*N*-dimethylbenzenesulfonamide;

2-(4-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1-(4-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)acetonitrile;

6-(4-(cyanomethyl)-4-(3-((4(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidin-1-yl)nicotinonitrile;

6-(4-(cyanomethyl)-4-(3-((4((difluoromethyl)sulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidin-1-yl)nicotinonitrile;

2-(4-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-1-(5(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)acetonitrile;

2-(1-(2,2-difluoropropanoyl)-4-(3-((4-(methylsulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)piperidin-4-yl)acetonitrile;

2-(4-(3-fluoroazetidin-1-yl)-1-(4-oxo-3-((4-(trifluoromethyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile;

2-(1-(4-oxo-3-((4-(trifluoromethyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(phenylamino)cyclohexyl)acetonitrile;

2-(4-hydroxy-1-(4-oxo-3-((4-(trifluoromethyl)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile;

2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(3-fluoroazetidin-1-yl)cyclohexyl)acetonitrile;

2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(3-methoxyazetidin-1-yl)cyclohexyl)acetonitrile;

2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-((2,2,2-trifluoroethyl)amino)cyclohexyl)acetonitrile;

2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-hydroxycyclohexyl)acetonitrile;

2-(1-(3-((4-chlorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(phenylamino)cyclohexyl)acetonitrile;

2-(4-(3-methoxyazetidin-1-yl)-1-(4-oxo-3-((4-(trifluoromethoxy)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile;

2-(1-(4-oxo-3-((4-(trifluoromethoxy)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(phenylamino)cyclohexyl)acetonitrile;

2-(4-(cyclohexylamino)-1-(4-oxo-3-((4-(trifluoromethoxy)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile;

2-(1-(3-((4-chloro-3-fluorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(cyclohexylamino)cyclohexyl)acetonitrile;

2-(1-(3-((4-chloro-3-fluorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(3-methoxyazetidin-1-yl)cyclohexyl)acetonitrile;

2-(1-(3-((4-chloro-3-fluorophenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(phenylamino)cyclohexyl)acetonitrile;

2-(1-(3-((4-((difluoromethyl)sulfonyl)phenyl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(3-fluoroazetidin-1-yl)cyclohexyl)acetonitrile;

4-((1-(1-(cyanomethyl)-4-(3-fluoroazetidin-1-yl)cyclohexyl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N,N*-dimethylbenzenesulfonamide;

2-(4-(3-fluoroazetidin-1-yl)-1-(3-((2-methyl-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-6-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile;

2-(4-(dimethylamino)-1-(3-((2-methyl-1,1-dioxido-2,3-dihydrobenzo-[*d*]isothiazol-6-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile;

2-(4-(3-fluoroazetidin-1-yl)-1-(3-((2-methyl-1,1-dioxido-2,3-dihy-drobenzo[*d*]isothiazol-6-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)cyclohexyl)acetonitrile;

2-(1-(3-((2-(*tert*-butyl)-1,1-dioxido-2,3-dihydrobenzo[*d*]isothiazol-5-yl)amino)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-1-yl)-4-(dimethylamino)cyclohexyl)acetonitrile; and

4-((1-(1-(cyanomethyl)-4-oxocyclohexyl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridin-3-yl)amino)-*N,N*-dimethylbenzenesulfonamide.

8. A pharmaceutical composition comprising a compound of Claim 1 or a pharamceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

9. A method for the treatment of a JAK-mediated disease comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Claim 1 or a pharmaceutically acceptable thereof.

10. A method of treating a condition in a mammal that can be ameliorated by the inhibition of Janus kinases JAK1 and JAK 2 which condition is selected from, arthritis, asthma and obstructive airways diseases, autoimmune diseases or disorders, and cancer comprising administering to the mammal in need of such treatment, a therapeutically effective amount of a compound according to Claim 1or a pharmaceutically acceptable salt or a stereoisomer thereof.

11. A method according to Claim 10, wherein said condition is arthritis.

12. A method according to Claim 10, wherein said condition is selected from rheumatoid arthritis, juvenile arthritis, and psoriatic arthritis.

13. A method according to Claim 10, wherein said condition is asthma or obstructive airways diseases.

14. A method according to Claim 13, wherein said condition is selected from: chronic asthma, late asthma, airway hyper-responsiveness, bronchitis, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, recurrent airway obstruction, and chronic obstruction pulmonary disease (COPD), and emphysema.

15. A method according to Claim 10, wherein said condition is autoimmune diseases or disorders.

16. A method of treating asthma in a mammal in need thereof, comprising administering a therapeutically effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

17. A method of treating arthritis in a mammal in need thereof, comprising administering a therapeutically effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

18. Use of a compound of Claim 1 or a pharmaceutically acceptable salt or a stereoisomer thereof in the manufacture of a medicament for the treatment of a disease or a disorder ameliorated by the inhibition of Janus kinases JAK1 and JAK 2.

19. Use of a compound of Claim 1 or a pharmaceutically acceptable salt or a stereoisomer thereof and a second active agent in the manufacture of a medicament for the treatment of a disease or a disorder ameliorated by the inhibition Janus kinases JAK1 and JAK 2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/072873

A. CLASSIFICATION OF SUBJECT MATTER

See the extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D471/-; C07D487/-; A61K31/-; A61P11/-; A61P17/-; A61P19/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPODOC, WPI, CNPAT, CNKI, CAPLUS(STN), MARPAT(STN): cyanoethyl, pyrazolo, pyridone?, pyridine?, JAK, janus kinase, inhibit+, structural search according to formula I.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/066061 A1(F. HOFFMANN-LA ROCHE AG et al.) 24 May 2012(24.05.2012) See the abstract and claims 1-22	1-19
A	WO 2013/036611 A1(INCYTE CORPORATION et al.) 14 March 2013(14.03.2013) See the abstract and claim 1.	1-19

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 November 2013(30.11.2013)	**26 Dec. 2013 (26.12.2013)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer JIANG, Shichao Telephone No. (86-10)82246761

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/072873

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9-17
because they relate to subject matter not required to be searched by this Authority, namely:
The subject matter of claims 9-17 relates to the method for treatment of human/animal body. However, the search has been carried out based on the alleged effects of the claims.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2013/072873

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO 2012/066061 A1	24.05.2012	CA 2817785 A1	24.05.2012
		CN 103313987 A	18.09.2013
		EP 2640722 A1	25.09.2013
		MX 2013005445 A	29.07.2013
		US 2013252941 A1	26.09.2013
WO 2013/036611 A1	14.03.2013	TW 201317246 A	01.05.2013
		US 2013060026 A1	07.03.2013

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2013/072873

Continuation of "**A. CLASSIFICATION OF SUBJECT MATTER**":

C07D471/04 (2006.01) i

C07D487/04 (2006.01) i

A61K31/37 (2006.01) i

A61K31/519 (2006.01) i

A61P11/02 (2006.01) i

A61P11/06 (2006.01) i

A61P17/06 (2006.01) i

A61P19/02 (2006.01) i