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(54) **Title**: CYCLOALKYLNITRILE PYRAZOLE CARBOXAMIDES AS JANUS KINASE INHIBITORS

(57) **Abstract**: Cycloalkylnitrile pyrazole carboxamides as JAK inhibitors useful for the treatment of JAK-mediated diseases such as rheumatoid arthritis, asthma, COPD and cancer are provided.

CYCLOALKYLNITRILE PYRAZOLE CARBOXAMIDES 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)). However, several adverse events have been reported that may be associated with inhibition of JAK2 signaling such as anemia, neutropenia and thrombocytopenia. Thus new or improved agents that selectively inhibit JAK1 activity but spare JAK2 activity are required for the treatment of several human diseases with an improved therapeutic index.

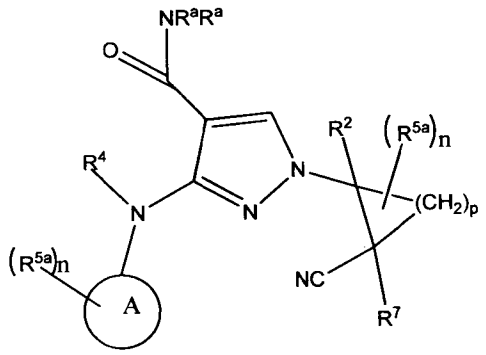
A considerable body of literature has accumulated that link the Jak/STAT pathway to various diseases and disorders including hyperproliferative disorders and cancer such as leukemia and lymphomas, immunological and inflammatory disorders such as transplant rejection, asthma, chronic obstructive pulmonary 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

R^a and R^4 are each independently selected from hydrogen and C_{1-4}alkyl;

A is selected from aryl, and heteroaryl;

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

p is 2, 3, or 4;

R^2 and R^7 are each independently selected from:

hydrogen,
halogen,
C_{1-10} alkyl,
C_{2-10} alkenyl,
C_{1-10} heteroalkyl,
aryl C_{0-10} alkylC_{0-10} alkyl,
C_{3-8} cycloalkylC_{0-10} alkyl,
heteroaryl C_{0-10} alkyl,
(C_{3-8})heterocycloalkyl C_{0-10} alkyl,

and wherein each of $\mathbf{R^2}$ and $\mathbf{R^7}$ are independently substituted with 0, 1, 2, 3, or 4 $\mathbf{R^{5a}}$ substituents;

$\mathbf{R^{5a}}$ 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,
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,
aryl C_{2-10} alkenyl$(oxy)_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,
aryl C_{2-10} alkynyl$(oxy)_{0-1}$(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_{1-10} heteroalkyl(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,
(C_{0-10})heteroalkylaminocarbonyloxy,
aryl (C_{0-10})alkylaminocarbonyloxy,
(C_{3-8})cycloalkyl(C_{0-10})alkylaminocarbonyloxy,
heteroaryl(C_{0-10})alkylaminocarbonyloxy,
(C_{3-8})heterocycloalkyl(C_{0-10})alkylaminocarbonyloxy,
C_{0-10} alkylamino$(oxy)_{0-1}$(carbonyl)$_{0-1}C_{2-10}$ alkenyl,
C_{1-10} alkylamino$(oxy)_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,

(C_{0-10})heteroalkylamin$(oxy)_{0-1}(carbonyl)_{0-1}C_{0-10}$ alkyl,
C_{3-8} cycloalkyl C_{0-10} alkylamino$(oxy)_{0-1}(carbonyl)_{0-1}C_{0-10}$ alkyl,
aryl C_{0-10}alkylamino$(oxy)_{0-1}(carbonyl)_{0-1}C_{0-10}$ alkyl,
heteroarylC_{0-10}alkylamino$((oxy)_{0-1}(carbonyl)_{0-1}C_{0-10}$ alkyl,
(C_{3-8})heterocycloalkylC_{0-10}alkylamino$(oxy)_{0-1}(carbonyl)_{0-1}C_{0-10}$ alkyl,
C_{1-10} alkyl$(oxy)_{0-1}(carbonyl)_{0-1}$amino$C_{0-10}$ alkyl,
C_{1-10} heteroalkyl $(oxy)_{0-1}(carbonyl)_{0-1}$amino$C_{0-10}$ alkyl,
C_{3-8} cycloalkyl C_{0-10} alkyl $(oxy)_{0-1}(carbonyl)_{0-1}$amino$C_{0-10}$ alkyl,
aryl C_{0-10} alkyl$(oxy)_{0-1}(carbonyl)_{0-1}$amino$C_{0-10}$ alkyl,
heteroaryl C_{0-10} alkyl$(oxy)_{0-1}(carbonyl)_{0-1}$amino$C_{0-10}$ alkyl,
(C_{3-8})heterocycloalkyl C_{0-10} alkyl$(oxy)_{0-1}(carbonyl)_{0-1}$amino$C_{0-10}$ alkyl,
$-CO_2(C_{0-10}$ alkyl),
$-(C_{0-10}$ alkyl)CO_2H,
Oxo (=O),
formyl,
sulfonyl,
C_{1-10} alkylsulfonyl,
C_{1-10} heteroalkylsulfonyl,
(C_{3-8}) cycloalkylsulfonyl,
(C_{3-8}) cycloheteroalkylsulfonyl,
heteroarylsulfonyl,
arylsulfonyl,
aminosulfonyl,
$-SO_2N(C_{0-6}alkyl)_{1-2}$,
$-SO_2C_{1-6}$alkyl,
$-SO_2CF_3$,
$-SO_2CF_2H$,
$-Si(CH_3)_3$
C_{1-10} alkylsulfinyl,
amino,
$(C_{0-10}$ alkyl$)_{1-2}$ amino,
C_{1-4}acylamino C_{0-10} alkyl,
hydroxyl,
$(C_{1-10}$ alkyl)OH,
C_{0-10} alkylalkoxyl,
imino$(C_{0-10}$alkyl),
$(C_{0-10}$alkyl)imino,

cyano,
C_{1-6}alkylcyano, and
C_{1-6}haloalkyl;
wherein two R^{5a} and the atom to which they are attached may optionally form a 3-, 4-, 5-, or 6- membered saturated ring system;
wherein R^{5a} is each optionally substituted with 1, 2, 3, or 4 R^6 substituents, and R^6 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,
aryl C_{2-10} alkenyl$(oxy)_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,
aryl C_{2-10} alkynyl$(oxy)_{0-1}$(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,
(C_{3-8})cycloalkyl(C_{0-10})alkylaminocarbonyloxy,
heteroaryl(C_{0-10})alkylaminocarbonyloxy,
(C_{3-8})heterocycloalkyl(C_{0-10})alkylaminocarbonyloxy,
C_{1-10} alkylamino$(oxy)_{0-1}$carbonylC_{0-10} alkyl,
C_{3-8} cycloalkyl C_{0-10} alkylamino$(oxy)_{0-1}$carbonylC_{0-10} alkyl,
aryl C_{0-10} alkylamino$(oxy)_{0-1}$carbonylC_{0-10} alkyl,
heteroaryl C_{0-10} alkylamino$(oxy)_{0-1}$carbonylC_{0-10} alkyl,
(C_{3-8})heterocycloalkyl C_{0-10} alkylamino$(oxy)_{0-1}$carbonylC_{0-10} alkyl,
C_{1-10} alkyl $(oxy)_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
C_{3-8} cycloalkyl C_{0-10} alkyl $(oxy)_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
aryl C_{0-10} alkyl$(oxy)_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,

heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
(C_{3-8})heterocycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
-CO_2(C_{0-10} alkyl),
-(C_{0-10} alkyl)CO_2H,
Oxo (=O),
Sulfonyl,
C_{1-10} alkylsulfonyl,
C_{1-10} heteroalkylsulfonyl,
(C_{3-8})cycloalkylsulfonyl,
(C_{3-8})cycloheteroalkylsulfonyl,
heteroarylsulfonyl,
arylsulfonyl,
aminosulfonyl,
-$SO_2N(C_{1-6}alkyl)_{1-2}$,
-SO_2C_{1-6}alkyl,
-SO_2CF_3,
-SO_2CF_2H,
C_{1-10} alkylsulfinyl,
-OSi(C_{1-10} alkyl)$_3$,
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,
imino(C_{0-10}alkyl),
(C_{0-10}alkyl)imino,
hydroxy,
(C_{1-10} alkyl)OH,
C_{1-10} alkoxy,
cyano, and
C_{1-6}haloalkyl;

wherein two $\mathbf{R^6}$ and the atoms to which they are attached may optionally form a 3-, 4-, 5-, or 6- membered saturated ring system; and

$\mathbf{R^6}$ 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, C_{1-10} heteroalkylsulfonyl, oxo (O=), (C_{3-8}) cycloalkylsulfonyl, (C_{3-8}) cycloheteroalkylsulfonyl, heteroarylsulfonyl, arylsulfonyl, aminosulfonyl,

$-SO_2N(C_{1-6}alkyl)_{1-2}$, $-SO_2C_{1-6}alkyl$, $-SO_2CF_3$, $-SO_2CF_2H$, $-C_{1-10}$ alkylsulfinyl, $-OSi(C_{1-10}alkyl)_3$, $-O_{(0-1)}(C_{1-10})$haloalkyl, amino$(C_{1-6}alkyl)_{0-2}$ and NH_2;

with the proviso that the compound of formula I is other than:

1-[(1R,2S,6S and 1S,2R,6R)-2-cyano-6-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-[(1S,2R and 1R,2S)-2-cyanocyclohexyl]-3-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1*H*-pyrazole-4-carboxamide; and

3-[(2-chloropyridin-4-yl)amino]-1-[(1S,2R and 1R,2S)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide.

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

1-[2-cyanocyclopentyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-{2-cyanocyclopentyl}-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-{[2-cyanocyclopentyl]}-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-{2-cyanocyclopentyl]}-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-((2-cyanocyclohexyl)-3-(phenylamino)-1H-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-(8-cyano-1,4-dioxaspiro[4.5]dec-7-yl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
methyl-3-[4-carbamoyl-3-(phenylamino)-1*H*-pyrazol-1-yl]-4-cyanocyclohexanecarboxylate;
1-[2-cyano-6-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-3-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-5-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
[4-({4-Carbamoyl-1-[2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]acetic acid;
[4-({4-carbamoyl-1-[2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]acetic acid;
1-[2-Cyano-4-hydroxycyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-Cyano-4-hydroxycyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-5-(dimethylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-5-(dimethylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;
1-{[2-cyano-5-(methylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;
1-{[5-(benzylamino)-2-cyanocyclohexyl}-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

tert-Butyl-4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexanecarboxylate;

methyl-4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexanecarboxylate;

1-2-Cyano-4-(hydroxymethyl)cyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-((4-(Aminomethyl)-2-cyanocyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-((2-Cyano-4-formylcyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-{2-Cyano-5,5-dimethylcyclohexyl}-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

tert-butyl [3-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-4-cyanocyclohexyl]carbamate;

1-(2-cyano-5-methylcyclohexyl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-(5-cyanospiro[2.5]octan-6-yl)-3-((2-fluoropyridin-4-yl)amino)-1*H*-pyrazole-4-carboxamide;

tert-butyl {[3-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-4-cyanocyclohexyl]methyl}carbamate;

tert-butyl {[3-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-4-cyanocyclohexyl]methyl}carbamate;

tert-butyl 3-(4-carbamoyl-3-(phenylamino)-1H-pyrazol-1-yl)-4-cyanocyclohexanecarboxylate;

1-[2-Cyano-4-hydroxycyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-Cyano-4-hydroxycyclohexyl]-3-({4-[(difluoromethyl) sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-Cyano-4-hydroxycyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[(2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

tert-butyl 4-[4-carbamoyl-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazol-1-yl]-3-cyanocyclohexanecarboxylate;

1-[2-Cyanocyclohexyl]-3-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-Cyanocyclohexyl]-3-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(methylcarbamoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-cyanophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(2-chloropyridin-4-yl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[3-fluoro-4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(difluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[(2-cyanocyclohexyl]-3-{[4-(ethylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(2,2,2-trifluoroethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(methylcarbamoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-cyanophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({3-(hydroxymethyl)-4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(6-fluoropyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[1-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-isoindol-5-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[1-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-isoindol-5-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[2-(1-methyl-1*H*-pyrazol-4-yl)pyridin-4-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(6-fluoropyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-formylphenyl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-bromophenyl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-acetylphenyl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[3,3,3-trifluoro-2-hydroxy-1,1-dimethylpropyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[3,3,3-trifluoro-2-hydroxy-1,1-dimethylpropyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({3-fluoro-4-[3,3,3-trifluoro-2-hydroxy-1,1-dimethylpropyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({6-[2,2,2-trifluoro-1-hydroxy-1-methylethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({6-[2,2-difluoro-1-hydroxyethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({6-[2,2-difluoro-1-hydroxy-1-methylethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(7-fluoroquinolin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(6-chloropyridin-3-yl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

2-[4-({4-carbamoyl-1-[2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]-2-methylpropanoic acid;

3-[(6-chloropyridin-3-yl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(6-chloropyridin-3-yl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-{[4-(aminomethyl)phenyl]amino}-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({6-[2,2,2-trifluoro-1-hydroxyethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide;

3-[(5-chloropyridin-3-yl)amino]-1-[(2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(6-fluoroquinolin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[(2-cyanocyclohexyl]-3-[(3,4-dichlorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({6-[2,2,2-trifluoro-1-hydroxyethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide;

3-[(3-chloro-5-fluorophenyl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

2-[4-({4-carbamoyl-1-[2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]-2-methylpropanoic acid;

1-[2-cyanocyclohexyl]-3-(pyridazin-4-ylamino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(3,5-dichlorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[6-(difluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(4-chloro-3-fluorophenyl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-{1,1-dimethyl-2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl}phenyl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(3-chloro-4-fluorophenyl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[6-(difluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(6-chloroquinolin-3-yl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(7-chloroquinolin-3-yl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(3-hydroxy-1,1-dioxido-2,3-dihydro-1-benzothiophen-5-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(1,1-dioxido-1-benzothiophen-5-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[(2-cyanocyclohexyl]-3-({4-[(difluoromethyl)sulfonyl]-3-(hydroxymethyl)phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(fluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(cyclopropylmethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(pyridin-2-ylsulfamoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(2-morpholin-4-ylethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

3-({4-[(4-benzylpiperidin-1-yl)sulfonyl]phenyl}amino)-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

methyl 5-({4-carbamoyl-1-[2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)pyridine-2-carboxylate;

N-tert-butyl-5-({4-carbamoyl-1-[2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)pyridine-3-carboxamide;

methyl 5-({4-carbamoyl-1-[2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)pyridine-3-carboxylate;

1-[2-cyanocyclohexyl]-3-[(5-methylpyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(5-cyanopyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(6-cyanopyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-b]pyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(6-cyano-5-methylpyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;

methyl 5-({4-carbamoyl-1-[2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)-3-methylpyridine-2-carboxylate;

1-[2-cyanocyclohexyl]-3-[(6-cyano-5-fluoropyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(6-cyclopropylpyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(pyridin-4-ylsulfamoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(cyclohexylsulfamoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

3-{[4-(benzylsulfamoyl)phenyl]amino}-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(pyridin-3-ylmethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(pyridin-2-ylmethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(pyridin-4-ylmethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(2-pyrrolidin-1-ylethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(2,6-dimethylphenyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

3-({4-[(4-acetylpiperazin-1-yl)sulfonyl]phenyl}amino)-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-({4-[(4-chlorobenzyl)sulfamoyl]phenyl}amino)-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(1,4-dioxa-8-azaspiro[4.5]dec-8-ylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(1-methylethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(quinolin-7-ylsulfamoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-{[4-(trifluoromethyl)phenyl]sulfamoyl}phenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-{[4-(trifluoromethyl)benzyl]sulfamoyl}phenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-{[4-(3-methoxyphenyl)piperazin-1-yl]sulfonyl}phenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(2-methoxyethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(morpholin-4-ylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(3,4-difluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(difluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-(2-Cyano-5-hydroxy-2-methylcyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-(2-cyano-5-fluoro-2-methylcyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-2-cyano-2-methylcyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-[2-Cyanocyclohexyl]-3-[(1,1-dioxido-2,3-dihydro-1-benzothiophen-5-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[(2-Cyanocyclohexyl]-3-{[5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[(2-cyanocyclohexyl]-3-{[6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[6-(1*H*-pyrazol-4-yl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-Cyano-4-fluorocyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-[6-cyanocyclohex-3-en-1-yl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-[2-Cyano-6-fluorocyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-(2-cyano-4(R)-hydroxycyclohexyl)-3-((4-(trifluoromethoxy)phenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(4-chloro-3-fluorophenyl)amino]-1-[2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-[(4-cyanophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-[(3,4-dichlorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(2-fluoro-1,1-dimethylethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(1-methoxy-1-methylethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(6-chloropyridin-3-yl)amino]-1-[2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-[(4-cyclopropylphenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[6-(difluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(3-methyloxetan-3-yl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-{[3-fluoro-4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(difluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
3-[(4-chlorophenyl)amino]-1-[2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-[2-Cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;
1-[(4-[4-carbamoyl-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazol-1-yl]-3-cyano-N,N-dimethylcyclohexanaminium trifluoroacetate;
1-[2-cyano-4-(methylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(ethylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(methylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide,
1-[2-cyano-4-(dimethylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(cyclopropylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-{2-cyano-4-[(2,2,2-trifluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-{2-cyano-4-[(2,2,2-trifluoroethyl)amino]cyclohexyl}-3-({4-[(difluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(morpholin-4-yl)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide;
1-{(2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2-hydroxyethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2-methoxyethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2-fluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2-fluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-[4-(Azetidin-1-yl)-2-cyanocyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-((4-(Azetidin-1-yl)-2-cyanocyclohexyl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-(4-(tert-butyl(methyl)amino)-2-cyanocyclohexyl)-3-((4-chlorophenyl)amino)-1H-pyrazole-4-carboxamide;

1-{2-cyano-4-[3-(1-hydroxy-1-methylethyl)azetidin-1-yl]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[1-cyclopropylethyl]amino}cyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2,4-dimethylazetidin-1-yl]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(cyclopropylmethyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(dimethylamino)cyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[1-cyclopropylethyl]amino}cyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(dimethylamino)cyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[6-(hydroxymethyl)-3-azabicyclo[3.1.0]hex-3-yl]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[(3-methyloxetan-3-yl)methyl]amino}cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(dimethylamino)cyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[(1-hydroxycyclopropyl)methyl]amino}cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(4-chloro-3-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-chloro-3-fluorophenyl)amino]-1-2-cyano-4-(dimethylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chloro-3-fluorophenyl)amino]-1-[(2-cyano-4-(methylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(methylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

3-[(4-chloro-3-fluorophenyl)amino]-1-[2-cyano-4-{[1-cyclopropylethyl]amino}cyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-({4-[(2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[6-(difluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[4-(tert-butylamino)-2-cyanocyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[4-(2,2,2-trifluoroethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(dimethylamino)cyclohexyl]-3-{[4-(trifluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[1-cyclopropylethyl]amino}cyclohexyl]-3-{[4-(trifluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[4-(trifluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

3-[(3-chloro-4-fluorophenyl)amino]-1-{2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

1-[(4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(4-formylphenyl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-chloro-3-fluorophenyl)amino]-1-[2-cyano-4-{[1-cyclopropylethyl]amino}cyclohexyl]-1*H*-pyrazole-4-carboxamide;

2-[4-({1-[(4-azetidin-1-yl-2-cyanocyclohexyl]-4-carbamoyl-1*H*-pyrazol-3-yl}amino)phenyl]-2-methylpropanoic acid;

2-[4-({1-[4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-4-carbamoyl-1*H*-pyrazol-3-yl}amino)phenyl]-2-methylpropanoic acid;

1-[2-cyano-4-(oxetan-3-ylamino)cyclohexyl]-3-{[4-(2,2,2-trifluoroethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(4-acetylphenyl)amino]-1-[4-azetidin-1-yl-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(dimethylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(3-methylazetidin-1-yl)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[4-(benzylamino)-2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{[1-cyclopropylethyl]amino}cyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3-methoxyazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(4-chlorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[4-(difluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3-fluoroazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2,2,2-trifluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[4-(difluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(4-chlorophenyl)amino]-1*H*-pyrazole-4-carboxamide;
1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;
1-{2-cyano-4-[(2,2,2-trifluoroethyl)amino]cyclohexyl}-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(3-fluoroazetidin-1-yl)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-{2-cyano-4-[(2,2-difluoroethyl)(methyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-{2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-3-[(4-cyanophenyl)amino]-1*H*-pyrazole-4-carboxamide;
3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(dimethylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(2-oxa-6-azaspiro[3.3]hept-6-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(3-methylazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-{2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-3-({4-[(difluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(dimethylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(dimethylamino)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;
1-[4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-[4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(dimethylamino)cyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-[4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(cyclopropylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(cyclopropylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3-methylazetidin-1-yl)cyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide,

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(6-oxa-1-azaspiro[3.3]hept-1-yl)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3-methoxyazetidin-1-yl)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[2-(methylsulfonyl)ethyl]amino}cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2-methoxyethyl)(methyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3-hydroxyazetidin-1-yl)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[(1,1-dioxidotetrahydrothiophen-3-yl)methyl]amino}cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(1,1-dioxidotetrahydrothiophen-3-yl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[2-(dimethylsulfamoyl)ethyl]amino}cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(oxetan-3-ylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2R)-2-(fluoromethyl)pyrrolidin-1-yl]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(3S)-3-fluoropyrrolidin-1-yl]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

N-{4-[4-carbamoyl-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazol-1-yl]-3-cyanocyclohexyl}glycine;

1-{2-cyano-4-[(dicyclopropylmethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(3,3,3-trifluoropropyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[methyl(3,3,3-trifluoropropyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(cyclopropylmethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(1-methylethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[1-cyclopropylethyl]amino}cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(dicyclopropylmethyl)(methyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(dicyclopropylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[1-cyclopropylethyl]amino}cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3-methylazetidin-1-yl)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(dimethylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[1-cyclopropylethyl]amino}cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[1-cyclopropyl-2,2,2-trifluoroethyl]amino}cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(2,2-dimethylazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[(2-cyano-4-(3-hydroxy-3-methylazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[3-hydroxy-3-(trifluoromethyl)azetidin-1-yl]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[4-(tert-butylamino)-2-cyanocyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(1-methylcyclopropyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(3-methyloxetan-3-yl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(1-cyclopropyl-1-methylethyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(2-hydroxy-1,1-dimethylethyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{(2-cyano-4-[3-(1-hydroxy-1-methylethyl)azetidin-1-yl]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[3-hydroxy-3-(trifluoromethyl)azetidin-1-yl]cyclohexyl}-1H-pyrazole-4-carboxamide;

1-{2-cyano-4-[(1-cyclopropyl-1-methylethyl)amino]cyclohexyl}-3-(phenylamino)-1H-pyrazole-4-carboxamide;

1-[4-(tert-butylamino)-2-cyanocyclohexyl]-3-(phenylamino)-1H-pyrazole-4-carboxamide;

1-{2-cyano-4-[(1-methylcyclopropyl)amino]cyclohexyl}-3-(phenylamino)-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[(2-cyano-4-{[(3-methyloxetan-3-yl)methyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{methyl[(3-methyloxetan-3-yl)methyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{[(1-hydroxycyclopropyl)methyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(2-hydroxy-2-methylpropyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{[1-(hydroxymethyl)cyclopropyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-2-cyano-4-[(2,2,2-trifluoroethyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[(2-cyano-4-{[1-(trifluoromethyl)cyclopropyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(2-methoxy-2-methylpropyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(1-cyclopropyl-1-methylethyl)(methyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

1-{2-cyano-4-[(3-methyloxetan-3-yl)amino]cyclohexyl}-3-(phenylamino)-1H-pyrazole-4-carboxamide;

1-{(2-cyano-4-[(2-methoxy-1,1-dimethylethyl)amino]cyclohexyl}-3-(phenylamino)-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{(2-cyano-4-[methyl(3-methyloxetan-3-yl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

1-{2-cyano-4-[methyl(2,2,2-trifluoroethyl)amino]cyclohexyl}-3-[(2-fluoropyridin-4-yl)amino]-1H-pyrazole-4-carboxamide;

1-{2-cyano-4-[methyl(2,2,2-trifluoroethyl)amino]cyclohexyl}-3-[(2-fluoropyridin-4-yl)amino]-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(2-methoxy-1,1-dimethylethyl)(methyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(4-methyltetrahydro-2H-pyran-4-yl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(2-methoxyethyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[(2-cyano-4-{[(1S)-2-methoxy-1-methylethyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(2-methoxyethyl)(methyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{[2-methoxy-1-methylethyl](methyl)amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{[2-methoxy-1-methylethyl](methyl)amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

4-{4-Carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexanaminium trifluoroacetate;

1-{2-Cyano-4-[methyl(oxetan-3-yl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(cyclopropylmethyl)(methyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-({[3-(1-hydroxy-1-methylethyl)cyclobutyl]methyl}amino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[(2-cyano-4-(spiro[3.4]oct-2-ylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[cyclobutyl(cyclopropylmethyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2-methylpropyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[cyclobutyl(methyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(cyclopropylmethyl)(2-methylpropyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(cyclopropylmethyl)(oxetan-3-yl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{(2-cyano-4-[(2,6-difluorobenzyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[(2-cyano-4-(cyclobutylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{4-[bis(cyclopropylmethyl)amino]-2-cyanocyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(cyclobutylmethyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(oxetan-3-ylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-(4-(4-carbamoyl-3-((4-(trifluoromethyl)phenyl)amino)-1*H*-pyrazol-1-yl)-3-cyanocyclohexyl)-1-methylazetidin-1-ium 2,2,2-trifluoroacetate;

1-[4-{4-carbamoyl-3-[(4-chlorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl]-1-methylazetidinium;

1-[4-{4-carbamoyl-3-[(4-chlorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl]-1-ethylazetidinium;

1-[4-{4-carbamoyl-3-[(4-chlorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl]-1,3,3-trimethylazetidinium;

1-[4-{4-carbamoyl-3-[(4-chlorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl]-1-(cyclopropylmethyl)azetidinium;

3-[(4-Chloro-3-fluorophenyl)amino]-1-[2-cyano-4-cyclopropyl-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxy-4-methylcyclohexyl]-3-{[4-(3,3,3-trifluoro-hydroxy-1,1-dimethylpropyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxy-4-methylcyclohexyl]-3-{[4-(3,3,3-trifluoro-hydroxy-1,1-dimethylpropyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-ethenyl-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chloro-3-fluorophenyl)amino]-1-[2-cyano-4-hydroxy-4-methylcyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxy-4-methylcyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-hydroxy-4-methylcyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-cyclopropyl-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-(2-Cyano-4-hydroxycyclohexyl)-3-((4-(trifluoromethoxy)phenyl)amino)-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chloro-3-fluorophenyl)amino]-1-[2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-[(4-cyanophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[6-(difluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[(2-cyano-4-hydroxycyclohexyl]-3-{[4-(3,3,3-trifluoro-hydroxy-1,1-dimethylpropyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-[(4-cyclopropylphenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(3-methyloxetan-3-yl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-[(3,4-dichlorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(2-fluoro-1,1-dimethylethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

4-{4-Carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl phenylcarbamate;

4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl cyclohexylcarbamate;

4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl phenylcarbamate;

4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl propan-2-ylcarbamate;

4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl methylcarbamate;

4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl ethylcarbamate;

3-((4-chlorophenyl)amino)-1-(2-cyano-4-(3,3-dimethylazetidine-1-carbonyl)cyclohexyl)-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{[3-(1-hydroxy-1-methylethyl)azetidin-1-yl]carbonyl}cyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[4-(2-azaspiro[3.3]hept-2-ylcarbonyl)-2-cyanocyclohexyl]-3-[(4-chlorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(dicyclopropylmethyl)carbamoyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(3,3-difluoroazetidin-1-yl)carbonyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(oxetan-3-ylcarbamoyl)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{[3-(methylsulfonyl)azetidin-1-yl]carbonyl}cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(2,2,2-trifluoroethyl)carbamoyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(cyclobutylcarbamoyl)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{[1-cyclopropyl-2,2,2-trifluoroethyl]carbamoyl}cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(3,3-difluorocyclobutyl)carbamoyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(cyclopropylcarbamoyl)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(3-hydroxy-3-methylazetidin-1-yl)carbonyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(3,3-difluoropyrrolidin-1-yl)carbonyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{[(3-methyloxetan-3-yl)methyl]carbamoyl}cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(3-fluoroazetidin-1-yl)carbonyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

1-[4-(tert-butylcarbamoyl)-2-cyanocyclohexyl]-3-[(4-chlorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(2-oxa-6-azaspiro[3.3]hept-6-ylcarbonyl)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-(4-Chlorophenylamino)-1-(2-cyano-4-(2-hydroxypropan-2-yl)cyclohexyl)-1*H*-pyrazole-4-carboxamide;

1-[2-Cyano-4-(fluoromethyl)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-{2-Cyano-4-[(methylsulfonyl)amino]cyclohexyl}-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(methylsulfonyl)amino]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[methyl(methylsulfonyl)amino]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

1-[2-Cyanocyclohexyl]-3-({4-[(methoxyimino)methyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-Cyanocyclohexyl]-3-{[4-(N-methoxyethanimidoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

4-(4-Carbamoyl-3-((4-(trifluoromethyl)phenyl)amino)-1*H*-pyrazol-1-yl)-5-cyano-2-hydroxycyclohexyl acetate;

1-[2-Cyanocyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-Cyanocyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(difluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(2,2,2-trifluoroethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

tert-Butyl [3-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-4-cyanocyclohexyl]carbamate;

1-[8-Cyano-1,4-dioxaspiro[4.5]dec-7-yl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide; and

1-[2-cyanocyclohexyl]-3-[(1,1-dioxido-2,3-dihydro-1-benzothiophen-5-yl)amino]-1*H*-pyrazole-4-carboxamide.

In one embodiment of the invention, representative compounds include, but are not limited to the following compounds and their pharmaceutically acceptable salts and stereoisomers thereof:

1-(2-cyanocyclohexyl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-[2-Cyano-4-hydroxycyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[(2-cyanocyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({6-[2,2-difluoro-1-hydroxy-1-methylethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-b]pyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-(2-cyano-5-fluoro-2-methylcyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-(2-cyano-4-hydroxycyclohexyl)-3-((4-(trifluoromethoxy)phenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(difluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2-fluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2-fluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-(4-(Azetidin-1-yl)-2-cyanocyclohexyl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-(4-(*tert*-Butylamino)-2-cyanocyclohexyl)-3-((4-chlorophenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(4-chloro-3-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(methylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chloro-3-fluorophenyl)amino]-1-[2-cyano-4-(dimethylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(4-chlorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(dimethylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{1-cyclopropylethyl]amino}cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[methyl(3-methyloxetan-3-yl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

1-[2-cyano-4-({[3-(1-hydroxy-1-methylethyl)cyclobutyl]methyl}amino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-(2-cyano-4-hydroxycyclohexyl)-3-((4-(trifluoromethoxy)phenyl)amino)-1*H*-pyrazole-4-carboxamide; and

1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide.

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_{1-6} 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_{1-6} 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_{1-4} 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.

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 one or more of the carbon atoms is substituted by a heteroatom independently selected 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.

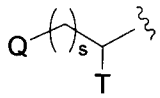
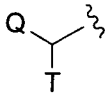
"Alkynyl" refers to an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and having the indicated number of carbon atoms. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl.

"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

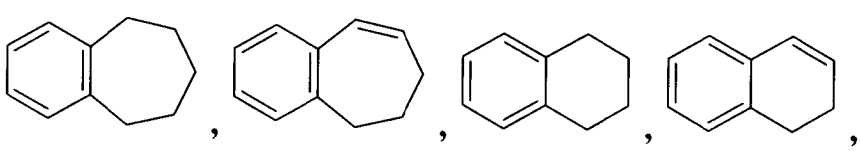
by a bond. For example, in the structure  , wherein s is an integer equal to zero, 1 or 2, the structure is  when s is zero.

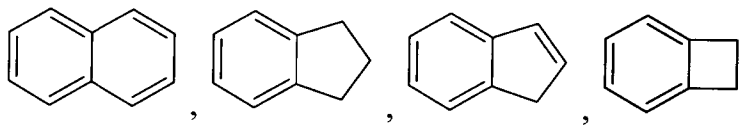
The term "C_{3-8} cycloalkyl" (or "C_3-C_8 cycloalkyl") means a cyclic ring of an alkane having three to eight total carbon atoms (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl). The terms "C_{3-7} cycloalkyl", "C_{3-6} cycloalkyl", "C_{5-7} cycloalkyl" and the like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

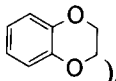
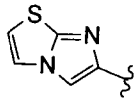
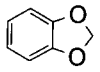
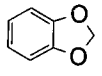
Examples of heterocycles (heterocyclyl) include, but are not limited to, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, dihydroimidazolyl, dihydroindolyl, 1,2,3,4-tetrahydroisoquinolinyl, 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.

"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.

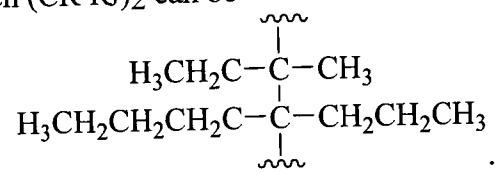
The term "substituted" (e.g., as in "aryl which is optionally substituted with one or more substituents ...") includes mono- and poly-substitution by a named substituent to the extent such single and multiple substitution (including multiple substitution at the same site) is chemically allowed.

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."

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 Ri and Rj are independently selected from the group consisting of methyl, ethyl, propyl and butyl, then $(CR^iR^j)_2$ can be



In one embodiment of the invention, $\mathbf{R^a}$ is hydrogen or methyl. In a variant of this embodiment, $\mathbf{R^a}$ is hydrogen.

In one embodiment of the invention $\mathbf{R^4}$ is hydrogen or methyl. In a variant of this embodiment, $\mathbf{R^4}$ is hydrogen. In another embodiment $\mathbf{R^4}$ is methyl.

In one embodiment, **p** is 2 or 3.

In one embodiment, $\mathbf{R^2}$ and $\mathbf{R^7}$ are each independently selected from hydrogen, halogen, $C_{1\text{-}10}$ alkyl, and $C_{3\text{-}8}$ cycloalkyl$C_{0\text{-}10}$ alkyl. In a variant of this embodiment, $\mathbf{R^2}$ and $\mathbf{R^7}$ are each independently selected from hydrogen, halogen, and $C_{1\text{-}10}$ alkyl.

In yet a further embodiment, $\mathbf{R^2}$ and $\mathbf{R^7}$ are each independently selected from hydrogen, and $C_{1\text{-}10}$ alkyl. In one embodiment of the invention, $\mathbf{R^2}$ and $\mathbf{R^7}$ are each independently selected from hydrogen, ethyl, propyl, butyl, pentyl, or methyl. In a variant of this embodiment, $\mathbf{R^2}$ and $\mathbf{R^7}$ are each independently selected from hydrogen or methyl. In another variant, $\mathbf{R^2}$ is hydrogen.

In one embodiment **A** is selected from: furanyl, thienyl, 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, 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, furopyridinyl, thienopyridinyl, benzotriazolyl, indolyl, isoindolyl, indazolyl, indolinyl, isoindolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, chromanyl, isochromanyl, tetrahydroquinolinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, quinolinyl, pyridazinyl, 2,3-dihydro-1-benzothiophenyl, 6,7-dihydro-5*H*-pyrrolo[3,4-b]pyridinyl and 2,3-dihydrobenzo[*b*]thiophenyl. 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo-1,4-dioxinyl, imidazo(2,1-b)(1,3)thiazole, and benzo-1,3-dioxolyl, phenyl, indenyl, and naphthyl.

In one embodiement, **A** is selected from phenyl, pyrindinyl, 1,2,3,4-tetrahydroquinolinyl, isoindolyl, indolyl, 2,3-dihydro-1*H*-isoindolyl, quinolinyl, pyridazinyl, 2,3-dihydro-1-benzothiophenyl, benzothiophenyl, 6,7-dihydro-5*H*-pyrrolo[3,4-b]pyridinyl, pyrrolo[3,4-b]pyridinyl, benzo[b]thiophenyl, and 2,3-dihydrobenzo[*b*]thiophenyl.

In one embodiement, **A** is selected from phenyl, pyrindinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, quinolinyl, pyridazinyl, 2,3-dihydro-1-benzothiophenyl, 6,7-dihydro-5*H*-pyrrolo[3,4-b]pyridinyl and 2,3-dihydrobenzo[*b*]thiophenyl.

In one embodiment, $\mathbf{R^{5a}}$ 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,
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,
aryl C_{2-10} alkenyl$(oxy)_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,
aryl C_{2-10} alkynyl$(oxy)_{0-1}$(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_{1-10} heteroalkyl(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})heterocycloalkyl C_{0-10} alkyl(carbonyl)$_{0-1}$oxyC_{0-10} alkyl,
$((C_{0-10})alkyl)_{1-2}$aminocarbonyloxy, aryl (C_{0-10})alkylaminocarbonyloxy,
C_{0-10} alkylamino$(oxy)_{0-1}$(carbonyl)$_{0-1}C_{2-10}$ alkenyl,
C_{1-10} alkylamino$(oxy)_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,
heteroarylC_{0-10}alkylamino$((oxy)_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,
(C_{3-8})heterocycloalkylC_{0-10}alkylamino$(oxy)_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,
C_{0-10} alkyl$(oxy)_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
C_{3-8} cycloalkyl C_{0-10} alkyl $(oxy)_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
aryl C_{0-10} alkyl$(oxy)_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
heteroaryl C_{0-10} alkyl$(oxy)_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
(C_{3-8})heterocycloalkyl C_{0-10} alkyl$(oxy)_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
$-CO_2(C_{0-10}$ alkyl),
$-(C_{0-10}$ alkyl)CO_2H,
Oxo (=O),
formyl,
sulfonyl,
C_{1-10} alkylsulfonyl,
C_{1-10}heteroalkylsulfonyl,
(C_{3-8}) cycloalkylsulfonyl,

(C_{3-8}) cycloheteroalkylsulfonyl,
heteroarylsulfonyl,
arylsulfonyl,
aminosulfonyl,
$-SO_2N(C_{0-6}alkyl)_{1-2}$,
$-SO_2C_{1-6}alkyl$,
$-SO_2CF_3$,
$-SO_2CF_2H$,
$-Si(CH_3)_3$,
C_{1-10} alkylsulfinyl,
amino,
$(C_{0-10}$ alkyl$)_{1-2}$ amino,
C_{1-4}acylamino C_{0-10} alkyl,
hydroxy,
$(C_{1-10}$ alkyl$)OH$,
C_{0-10} alkylalkoxyl,
imino(C_{0-10}alkyl),
(C_{0-10}alkyl)imino,
cyano,
C_{1-6}alkylcyano, and
C_{1-6}haloalkyl; wherein two $\mathbf{R^{5a}}$ and the atom to which they are attached may optionally form a 3-, 4-, 5-, or 6- membered saturated ring system and wherein $\mathbf{R^{5a}}$ is each optionally substituted with 1, 2, 3, or 4 $\mathbf{R^6}$ substituents.

In yet another embodiment, $\mathbf{R^{5a}}$ 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,
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,
aryl C_{0-10} alkyl (carbonyl)$_{0-1}$oxyC_{0-10} alkyl,
aryl (C_{0-10})alkylaminocarbonyloxy,
C_{1-10} alkylamino$(oxy)_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,
heteroarylC_{0-10}alkylamino((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_{3-8} cycloalkyl C_{0-10} alkyl (oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,

aryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
(C_{3-8})heterocycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
-CO_2(C_{0-10} alkyl),
-(C_{0-10} alkyl)CO_2H,
Oxo (=O),
formyl,
sulfonyl,
C_{1-10} alkylsulfonyl,
C_{1-10} heteroalkylsulfonyl,
(C_{3-8}) cycloalkylsulfonyl,
(C_{3-8}) cycloheteroalkylsulfonyl,
heteroarylsulfonyl,
arylsulfonyl,
aminosulfonyl,
-SO_2N(C_{0-6}alkyl)$_{1-2}$,
-SO_2C_{1-6}alkyl,
-SO_2CF_3,
-SO_2CF_2H,
-$Si(CH_3)_3$,
(C_{0-10} alkyl)$_{1-2}$ amino,
hydroxy,
(C_{1-10} alkyl)OH,
C_{0-10} alkylalkoxyl,
imino(C_{0-10}alkyl),
(C_{0-10}alkyl)imino,
cyano,
C_{1-6}alkylcyano, and
C_{1-6}haloalkyl;

wherein two $\mathbf{R^{5a}}$ and the atom to which they are attached may optionally form a 3-, 4-, 5-, or 6-membered saturated ring system and wherein $\mathbf{R^{5a}}$ is each optionally substituted with 1, 2, 3, or 4 $\mathbf{R^6}$ substituents.

In another embodiment of the invention, $\mathbf{R^{5a}}$ is selected from: methylsulfonyl, hydroxyl, trimethylsilyl, ethoxy, methoxy, methyloxycarbonyl, methylCOOH, hydroxycarbonylmethyl, methyloxycarbonyl, dimethylamino, fluoro, phenylcarbonyloxy, methylamino, oxo, ethylamino, benzylamino, t*ert*-butyloxycarbonyl, methoxycarbonyl, hydroxymethyl, aminomethyl, oxymethyl, methyl, methylaminomethyl, methylaminocarbonyl,

oxycarbonylamino, methyloxycarbonyl, ethyloxycarbonylamino, *tert*-butyloxycarbonylamino, ethyl, methyl, *tert*-butyloxycarbonylaminomethyl, carbonylamino, trifluoromethylsulfonyl, trifluoromethyl, trifluoroethyl, chloro, pyridinylaminocarbonyl, methylcarbonylamino, cyano, 1,2,4-oxadiazolyl, ethylsulfonyl, oxo, pyrazolyl, formyl (C=O), bromo, carbamoyl, acetyl, 3,3,3-trifluoro-1,1-dimethylpropyl, trifluoropentyl, 2,2,2-trifluoromethylethyl, difluoromethyl, 2,2-difluoromethylethyl, isopropyl, aminomethyl, methylethylcarbonylamino, *tert*-butylaminocarbonyl, cyclopropyl, sulfamoyl, (methylethyl)sulfamoyl, methylsulfamoyl, ethylsulfamoyl, piperazinylsulfonyl, piperidinylsulfonyl, pyridinylsulfonyl, morpholinylsulfonyl, difluoromethoxy, pyrazolyl, oxetanyl, cyclopropylmethoxy, dimethylamino, cyclopropylamino, morpholinyl, sulfonyl, azetidinyl, *tert*-butylamino, hydroxymethylethyl, (cyclopropylethyl)amino, (cyclopropylmethyl)amino, trifluoroethylamino, pyrrolidinyl, (oxetanylmethyl)amino, hydroxycarbonylisopropyl, oxetanylamino, hydroxymethyl, methylcarbonyl, (ethyl)(methyl)amino, methoxyethylamino, (tetrahydrothiophenylmethyl)amino, propyl(methyl)amino, cyclopropylamino, (dimethylethyl)amino, methylamino, oxetanylmethylamino, tetrahydro-2H-pyranylamino, *tert*-butyloxycarbonylamino, cyclobutylamino, butylamino, cyclobutylmethylamino, dimethylpropyl, ethenyl, phenylaminocarbonyloxy, cyclohexylaminocarbonyloxy, propylaminocarbonyloxy, methylaminocarbonyloxy, ethylaminocarbonyloxy, cyclopropylmethlcarbamoyl, tert-butyloxycarbonyl, hydroxycarbonyl, cyclopropylmethylaminocarbonyl, azetidinylcarbonyl, oxetanycarbamoyl, ethylcarbamoyl, cyclobutylcarbamoyl, cyclopropylmethylcarbamoyl, methylcarbamoyl, oxetanylmethycarbamoyl, pyrrolidinylcarbonyl, *tert*-butylcarbamoyl, hydroxypropanyl, methyloxycarbonyl, iminoC1-10 alkyl, and C1-10 alkylimino, wherein two $\mathbf{R^{5a}}$ and the atom to which they are attached may optionally form a 3-, 4-, 5-, or 6- membered saturated ring system and wherein $\mathbf{R^{5a}}$ is each optionally substituted with 1, 2, 3, or 4 substituents, $\mathbf{R^6}$.

In one embodiment, $\mathbf{R^6}$ is independently selected from: halogen, C1-10 alkyl(oxy)0-1(carbonyl)0-1C0-10 alkyl, C1-10 heteroalkyl(oxy)0-1(carbonyl)0-1C0-10 alkyl, C2-10 alkenyl(oxy)0-1(carbonyl)0-1C0-10 alkyl, aryl C0-10 alkyl(oxy)0-1(carbonyl)0-1C0-10 alkyl, aryl C2-10 alkenyl(oxy)0-1(carbonyl)0-1C0-10 alkyl, aryl C2-10 alkynyl(oxy)0-1(carbonyl)0-1C0-10 alkyl, C3-8 cycloalkyl C0-10 alkyl(oxy)0-1(carbonyl)0-1C0-10 alkyl, heteroaryl C0-10 alkyl(oxy)0-1(carbonyl)0-1C0-10 alkyl, (C3-8)heterocycloalkyl C0-10 alkyl(oxy)0-1(carbonyl)0-1C0-10 alkyl, C1-10 alkyl(carbonyl)0-1oxyC0-10 alkyl, C2-10 alkenyl(carbonyl)0-1oxyC0-10 alkyl, C1-10 heteroalkyl(carbonyl)0-1oxyC0-10 alkyl, ((C0-10)alkyl)1-2aminocarbonyloxy, C1-10 alkylamino(oxy)0-1carbonylC0-10 alkyl, C1-10 alkyl (oxy)0-1(carbonyl)0-1aminoC0-10 alkyl, (C3-8)heterocycloalkyl C0-10 alkyl(oxy)0-1(carbonyl)0-1aminoC0-10 alkyl, -CO2(C0-10 alkyl), -(C0-10 alkyl)CO2H, Oxo (=O), Sulfonyl, C1-10 alkylsulfonyl, C1-10 heteroalkylsulfonyl,

(C_{3-8})cycloalkylsulfonyl, (C_{3-8})cycloheteroalkylsulfonyl, heteroarylsulfonyl, arylsulfonyl, aminosulfonyl, $-SO_2N(C_{1-6}alkyl)_{1-2}$, $-SO_2C_{1-6}alkyl$, $-SO_2CF_3$, $-SO_2CF_2H$, 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, imino$(C_{0-10}$alkyl), hydroxy, $(C_{1-10}$ alkyl$)OH$, C_{1-10} alkoxy, cyano, and C_{1-6}haloalkyl; wherein two $\mathbf{R^6}$ and the atoms to which they are attached may optionally form a 3-, 4-, 5-, or 6- membered saturated ring system and $\mathbf{R6}$ 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, C_{1-10} heteroalkylsulfonyl, oxo (O=), (C_{3-8}) cycloalkylsulfonyl, (C_{3-8}) cycloheteroalkylsulfonyl, heteroarylsulfonyl, arylsulfonyl, aminosulfonyl, $-SO_2N(C_{1-6}alkyl)_{1-2}$, $-SO_2C_{1-6}alkyl$, $-SO_2CF_3$, $-SO_2CF_2H$, $-C_{1-10}$ alkylsulfinyl, $-OSi(C_{1-10}alkyl)_3$, $-O_{(0-1)}(C_{1-10})$haloalkyl, amino$(C_{1-6}alkyl)_{0-2}$ and NH_2.

In another embodiment of the invention $\mathbf{R^6}$ is independently selected from: halogen, C_{1-10} alkyl$(oxy)_{0-1}(carbonyl)_{0-1}C_{0-10}$ 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, $-CO_2(C_{0-10}$ alkyl), Oxo (=O), sulfonyl, C_{1-10} alkylsulfonyl, (C_{3-8})cycloalkylsulfonyl, (C_{3-8})cycloheteroalkylsulfonyl, heteroarylsulfonyl, $-SO_2N(C_{1-6}alkyl)_{1-2}$, amino, $(C_{0-10}$ alkyl$)_{1-2}$ amino, hydroxy, $(C_{1-10}$ alkyl$)OH$, C_{1-10} alkoxy, and C_{1-6}haloalkyl; wherein two $\mathbf{R^6}$ and the atoms to which they are attached may optionally form a 3-, 4-, 5-, or 6- membered saturated ring system, and $\mathbf{R6}$ 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, C_{1-10} heteroalkylsulfonyl, oxo (O=), (C_{3-8}) cycloalkylsulfonyl, (C_{3-8}) cycloheteroalkylsulfonyl, heteroarylsulfonyl, arylsulfonyl, aminosulfonyl, $-SO_2N(C_{1-6}alkyl)_{1-2}$, $-SO_2C_{1-6}alkyl$, $-SO_2CF_3$, $-SO_2CF_2H$, $-C_{1-10}$ alkylsulfinyl, $-OSi(C_{1-10}alkyl)_3$, $-O_{(0-1)}(C_{1-10})$haloalkyl, amino$(C_{1-6}alkyl)_{0-2}$ and NH_2.

In one particular embodiment, $\mathbf{R^6}$ is independently selected from: methyl, sulfonyl, quinolinyl, oxo, ethyl, ethoxy, fluoro, chloro, propyl, ethanol, trifluoromethyl, hydroxy, 1-hydroxy-1-methylethyl, -COOH, trifluoroethyl, hydroxymethyl, methylsulfonyl, difluoromethyl, dimethylsulfamoyl, fluoromethyl, cyclopropyl, cyclobutyl, benzyl, piperidinyl, pyridinyl, morpholinyl, cyclohexyl, phenyl, pyrrolidinyl, piperazinyl, methoxy, *tert*-butylmethyl, dimethylamino, hydroxyethyl, methylcarbonyl, hydroxymethylethyl, cyclopropylmethyl and methyloxycarbonyl and and $\mathbf{R6}$ 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, C_{1-10} heteroalkylsulfonyl, oxo (O=), (C_{3-8}) cycloalkylsulfonyl, (C_{3-8}) cycloheteroalkylsulfonyl, heteroarylsulfonyl, arylsulfonyl, aminosulfonyl, -$SO_2N(C_1$-6alkyl$)_{1-2}$, -SO_2C_1-6alkyl, -SO_2CF_3, -SO_2CF_2H, -C_{1-10} alkylsulfinyl, -OSi(C_1-10alkyl)3, -O(0-1)(C_1-10)haloalkyl, amino(C_1-6alkyl)0-2 and NH_2.

In one embodiment, the compounds of the instant invention are selective JAK1 inhibitors relative to JAK2. The determination of relative selectivity for a given compound of JAK1 inhibition is defined as the relative ratio of the (JAK2 IC_{50} value/JAK1 IC_{50} value) is at least 2. In yet another embodiment, for a given compound, the relative ratios of the (JAK2 IC_{50} value/JAK1 IC_{50} value) is at least 5.

"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 and stereoisomers thereof.

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 or stereoisimer 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, 1-(2S, 3S and 2R, 3R)-3-cyclobutan-2-yl]-

3-(phenylamino)-1*H*-pyrazole-4-carboxamide, 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, 1-(2S, 3S or 2R, 3R)-3-cyclobutan-2-yl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide, the "or" indicates that chiral resolution of racemate into individual enantiomers was accomplished but the actual optical activity of the specific enantiomer was not 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.

Salts

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, 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 and subsets thereof, embodiments thereof, as well as specific compounds are meant to also include the pharmaceutically acceptable salts and the 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 or stereoisomers 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 or JAK3. 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 diseases 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 by the selective inhibition of a Janus kinase JAK1 relative to JAK 2.

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 the selective inhibition of a Janus kinase JAK1 relative to JAK 2.

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. Dosage unit forms will generally contain between from about 0.1 mg to about 0.4 g of an active ingredient, typically 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.

METHODS OF SYNTHESIS
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	acetonitrile
MeCN	acetonitrile
BAST	bis(2-methoxyethyl)aminosulfur trifluoride
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
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
LRMS	low resolution mass spectrometry
MeI	iodomethane
Me-THF	2-methyltetrahydrofuran
MgSO4	magnesium sulfate
MP-$(OAc)_3BH$	solid supported (macro porous) triacetoxyborohydride
MPLC	medium pressure liquid chromatography
NaH	sodium hydride

Na_2SO_4	sodium sulfate
NaBH4	sodium borohydride
$NaHCO_3$	sodium bicarbonate
NaOMe	sodium methoxide
$Pd_2(dba)_3$	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
X-Phos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
Me_4-^{t}Bu-X-Phos	di-*tert*-butyl[3,4,5,6-tetramethyl-2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane
NMO	4-methylmorpholine N-oxide
TPAP	tetra-n-propylammonium perruthenate (VII)
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

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

Ambient temperature is 15-25 ^{o}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.

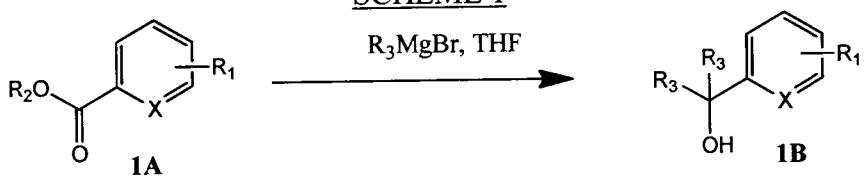
All end products were analyzed by NMR and LCMS.

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. Alkyl Grignard reagents are reacted with appropriately subtituted (hetero)aryl carboxylates **1A** at or around 0 °C in an appropriate solvent, such as THF, to afford intermediates **1B** used in the synthesis of examples of the instant invention.

SCHEME 1

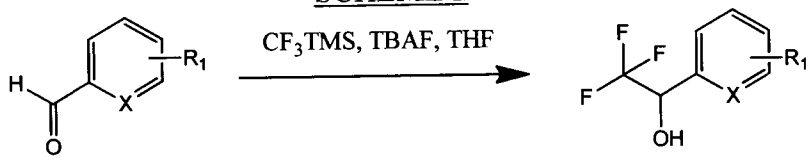


1A **1B**

Method 2

General procedures to prepare intermediates of the instant invention are described in Scheme 2. A trifluoromethyl anion equivalent, such as CF_3TMS, is reacted with TBAF and an appropriately substituted (hetero)aryl aldehyde **2A** in an appropriate solvent, such as THF, to yield intermediates **2B** used in the synthesis of examples of the instant invention.

SCHEME 2

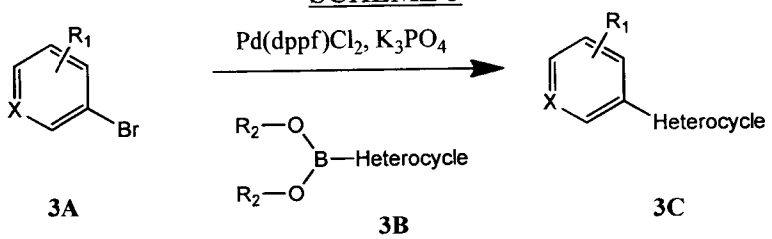


2A **2B**

Method 3

General procedures to prepare intermediates of the instant invention are described in Scheme 3. Heteroaryl boronate esters or boronic acids **3B** are cross coupled to optionally substituted (hetero)aryl bromides **3A** using a suitable palladium complex, such as $Pd(dppf)Cl_2$, and an appropriate base, such as K_3PO_4, in a compatible solvent or solvent mixture, such as 10:1 v:v dioxane:water, at or around 90 °C to yield intermediates **3C** in the synthesis of examples of the instant invention.

SCHEME 3



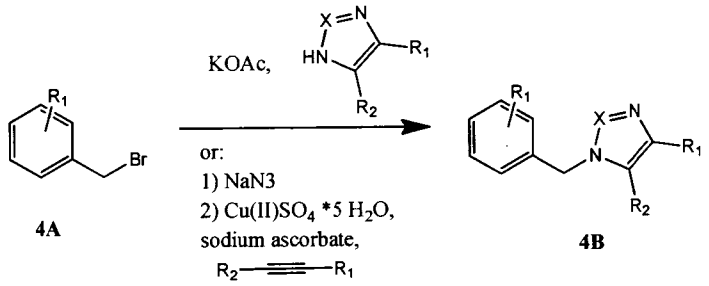
3A **3B** **3C**

Method 4

General procedures to prepare intermediates of the instant invention are described in Scheme 4. Appropriately substituted benzyl bromides **4A** can be reacted with aza heterocycles using a suitable base, such as potassium acetate, or be reacted with sodium azide followed by

optionally substituted acetylenes and standard "Click chemistry" reagents to afford intermediates **4B** in the synthesis of examples of the instant invention.

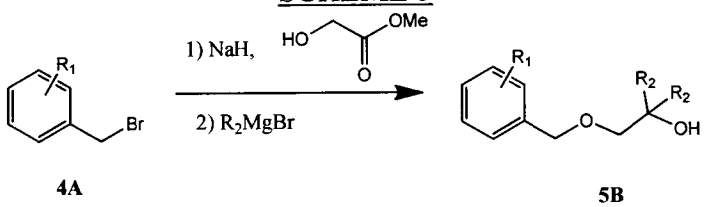
SCHEME 4



Method 5

General procedures to prepare intermediates of the instant invention are described in Scheme 5. Appropriately substituted benzyl bromides **4A** can be reacted with methyl hydroxy acetate in the presence of a suitable base, such as sodium hydride, and then further reacted with alkyl Grignard reagents to afford intermediates **5B** used in the synthesis of examples of the instant invention.

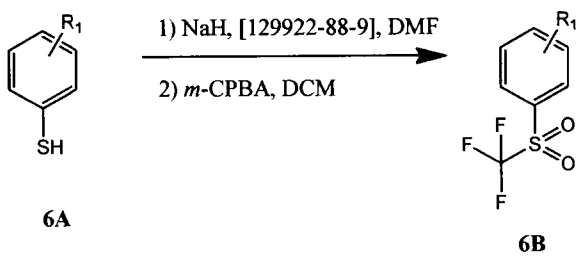
SCHEME 5



Method 6

General procedures to prepare intermediates of the instant invention are described in Scheme 6. Appropriately substituted thiophenols **6A** are reacted with a suitable base, such as sodium hydride, and a trifluoromethylating agent, such as 5-(trifluoromethyl)dibenzo[*b*,*d*]thiophenium trifluoromethanesulfonate at ambient temperature in an appropropiate solvent, such as DMF. The resulting intermediate is oxidized to the corresponding sulfone **6B** with a suitable oxidant, such as *m*-CPBA, to afford an intermediate used in the synthesis of examples of the instant invention.

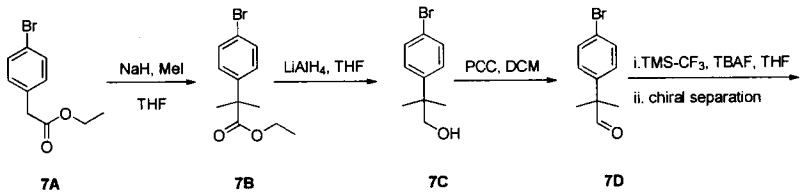
SCHEME 6

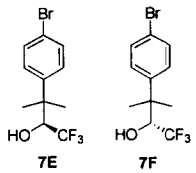


Method 7

General procedures to prepare intermediates of the instant invention are described in Scheme 7. Appropriately substituted phenylacetic esters **7A** are reacted with a suitable base, such as sodium hydride, and methylating agent, such as methyliodide at an appropriate temperature, in a suitable solvent, such as THF to provide **7B**. The resulting intermediate is reduced to alcohol **7C** with a suitable reducing agent, such as $LiALH_4$, which was subsequently oxidized to aldehyde **7D** with an oxidant such as PCC. Treatment of **7D** with CF_3 anion followed by resolution of enantiomers using chiral stationary phase chromatography afford intermediates **7E** and **7F** used in the synthesis of examples of the instant invention.

SCHEME 7

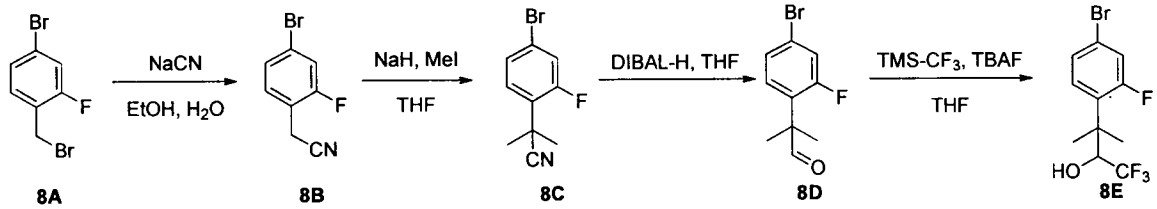




Method 8

General procedures to prepare intermediates of the instant invention are described in Scheme 8. Appropriately substituted benzylbromides **8A** are reacted with sodium cyanide in an appropriate solvent, such as aqueous ethanol to provide **8B**. The resulting intermediate is reacted with a suitable base, such as sodium hydride, and a methylating agent, such as methyliodide at an appropriate temperature in solvent, such as THF to provide **8C** which is subsequently reduced to aldehyde **8D** with a suitable reducing agent, such as DIBAL-H, in a suitable solvent such as THF. Treatment of **8D** with CF_3 anion afford intermediate **8E** used in the synthesis of examples of the instant invention.

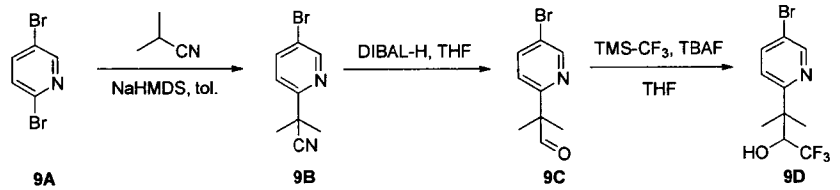
SCHEME 8



Method 9

General procedures to prepare intermediates of the instant invention are described in Scheme 9. 2-Cyanopropane is reacted with a suitable base, such as NaHMDS, in an appropriate solvent, such as toluene and reacted with 2,5-dibromopyridine **9A** to provide **9B** which is subsequently reduced to aldehyde **9C** with a suitable reducing agent, such as DIBAL-H, in a suitable solvent such as THF. Treatment of **9C** with CF_3 anion affords intermediate **9D** used in the synthesis of examples of the instant invention.

SCHEME 9

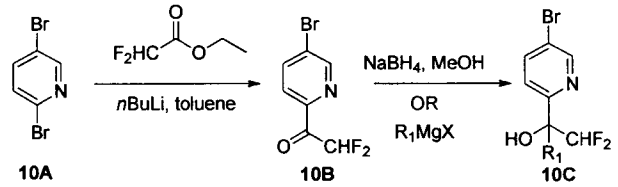


9A **9B** **9C** **9D**

Method 10

General procedures to prepare intermediates of the instant invention are described in Scheme 10. Difluoroacetate is reacted with a suitable base, such as n-BuLi, in an appropriate solvent, such as toluene and reacted with 2,5-dibromopyridine **10A** to provide **10B**. Ketone **10B** is subsequently reduced to alcohol **10C** (R_1 is hydrogen) with a suitable reducing agent, such as $NaBH_4$, in a suitable solvent such as methanol. Alternatively, ketone **10B** is reacted with a Grignard reagent to afford alcohol **10C** (R_1 is alkyl) used in the synthesis of examples of the instant invention.

SCHEME 10

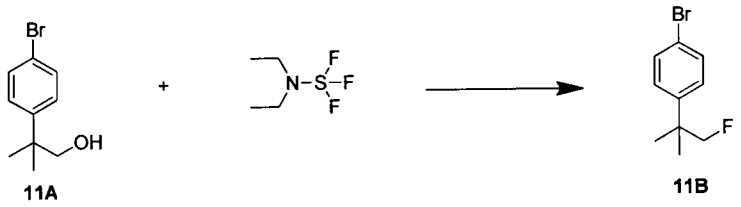


10A **10B** **10C**

Method 11

General procedures to prepare intermediates of the instant invention are described in Scheme 11. Alcohol **11A** is reacted with a nucleophillic fluoride source such as DAST to afford **11B** used in the synthesis of examples of the instant invention.

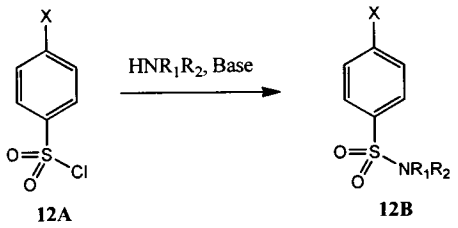
SCHEME 11



Method 12

General procedures to prepare intermediates of the instant invention are described in Scheme 12. Halo-substituted benzenesulfonyl chloride **12A** is reacted with amines in the presence of a base such as TEA to afford sulfonamides **12B** used in the synthesis of examples of the instant invention.

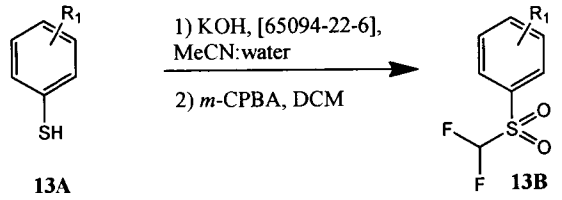
SCHEME 12



Method 13

General procedures to prepare intermediates of the instant invention are described in Scheme 13. Appropriately substituted thiophenols **13A** are reacted with a suitable base, such as potassium hydroxide, and a difluoromethylating agent, such as diethyl [bromo(difluoro)methyl]phosphonate, in an appropriate solvent or solvent mixture, such as 1:1 v:v MeCN:water. The resulting intermediate is oxidized to the corresponding sulfone **13B** with a suitable oxidant, such as *m*-CPBA, to afford an intermediate used in the synthesis of examples of the instant invention.

SCHEME 13



Method 14

General procedures to prepare intermediates of the instant invention are described in Scheme 14. Appropriately substituted aryl sulfoxides **14A** are reacted with a lewis acid, such as zinc iodide, and a suitable nucleophilic fluorine source, such as BAST, in a solvent, such as 1,2-DCE, at or around 40 °C. The resulting intermediate is oxidized to the corresponding sulfone

14B with a suitable oxidant, such as *m*-CPBA, to afford an intermediate used in the synthesis of examples of the instant invention.

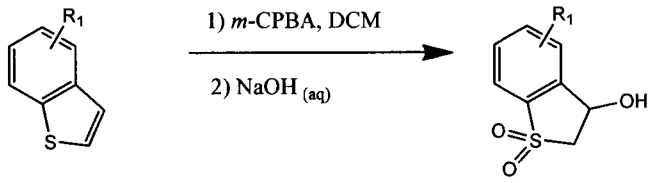
SCHEME 14

14A **14B**

Method 15

General procedures to prepare intermediates of the instant invention are described in Scheme 15. Appropriately substituted benzothiophenes **15A** are oxidized to the cooresponding sulfones with a suitable oxidant, such as *m*-CPBA, and then hydroxylated upon stirring in aqueous sodium hydroxide at at or around 100 °C to afford intermediates **15B** in the synthesis of examples of the instant invention.

SCHEME 15

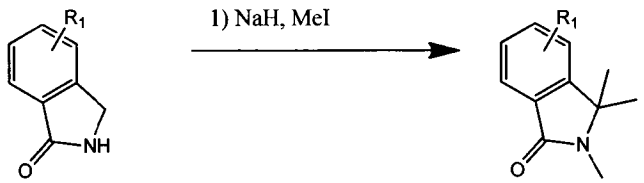


15A **15B**

Method 16

General procedures to prepare intermediates of the instant invention are described in Scheme 16. Appropriately substituted 2,3-dihydro-1*H*-isoindol-ones **16A** can be poly-methylated using a suitable base, such as sodium hydride, and methyl iodide to afford intermediates **16B** used in the synthesis of examples of the instant invention.

SCHEME 16



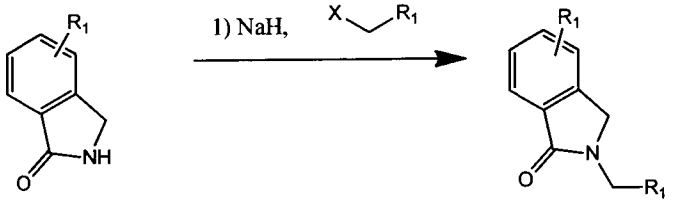
16A **16B**

Method 17

General procedures to prepare intermediates of the instant invention are described in Scheme 17. Appropriately substituted 2,3-dihydro-1*H*-isoindol-ones **16A** can be mono-

alkylated using a suitable base, such as sodium hydride, and optionally substituted alkylating agents to afford intermediates **17B** in the synthesis of examples of the instant invention.

SCHEME 17

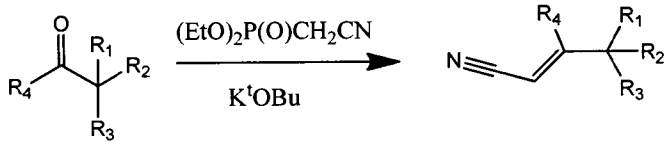


16A **17B**

Method 18

General procedures to prepare intermediates of the instant invention are described in Scheme 18. Optionally substituted alkyl aldehydes/ketones **18A** are condensed with diethyl (cyanomethyl)phosphonate in the presence of a suitable base, such as potassium *tert*-butoxide to yield substituted acrylonitriles **18B** used as intermediates in the synthesis of examples of the instant invention.

SCHEME 18

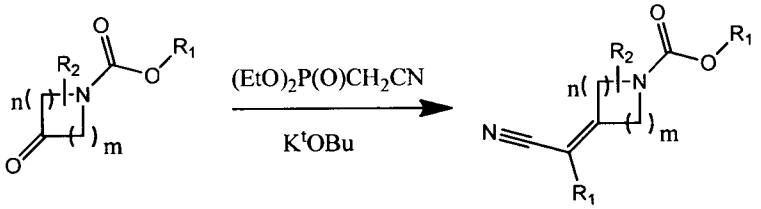


18A **18B**

Method 19

General procedures to prepare intermediates of the instant invention are described in Scheme 19. Optionally substituted carbamate protected heterocyclic ketones **19A** are condensed with diethyl (cyanomethyl)phosphonate in the presence of a suitable base, such as potassium *tert*-butoxide, to yield optionally substituted acrylonitriles **19B** used as intermediates in the synthesis of examples of the instant invention.

SCHEME 19



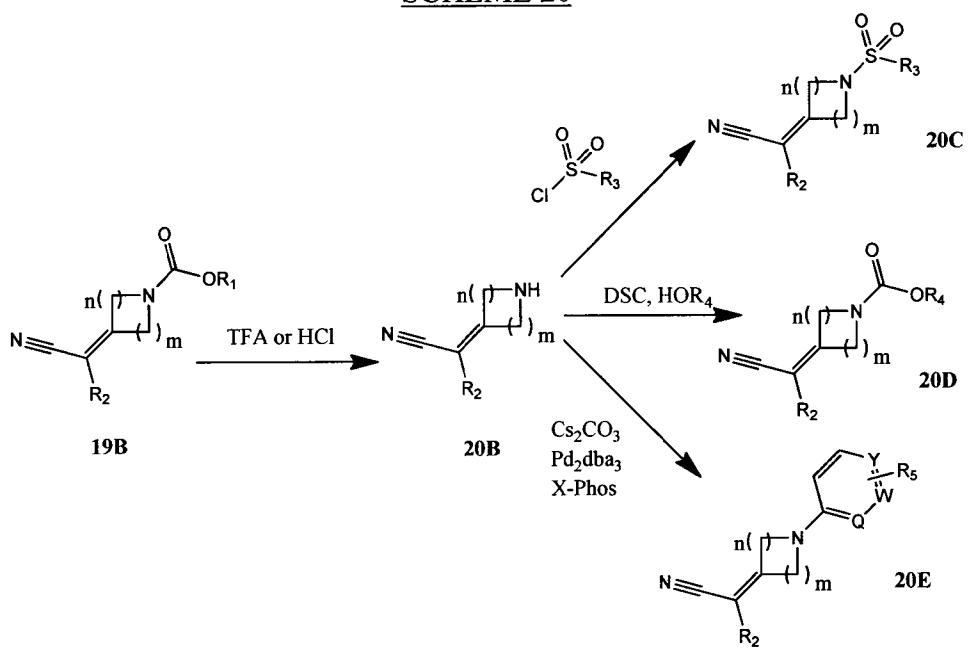
19A **19B**

Method 20

General procedures to prepare intermediates of the instant invention are described in Scheme 20. Carbamate protected optionally substituted acrylonitriles **19B** are deprotected in the presence of a suitable acid, such as TFA or HCl, to form amino intermediates **20B** that are

further derivatized to form sulfonamide **20C**, urethane **20D**, and N-arylated intermediates **20E**. Sulfonamide derivatives **20C** are formed by reacting deprotected optionally substituted acrylonitriles with optionally substituted sulfoyl chlorides in a suitable solvent, such as DCM, using an appropriate base, such as DIPEA. Urea derivatives **20D** are formed by reacting deprotected optionally substituted acrylonitriles with a doubly activated carbonyl equivalent, such as DSC, and optionally substituted alcohols in the presence of a suitable base, such as TEA. N-arylated derivatives **20E** are formed by reacting deprotected optionally substituted acrylonitriles with optionally substituted aryl halides using a suitable palladium-ligand system, such as $Pd_2(dba)_3$ and X-Phos, an appropriate base, such as Cs_2CO_3, in a solvent, such as *t*-BuOH, at or around 90 °C.

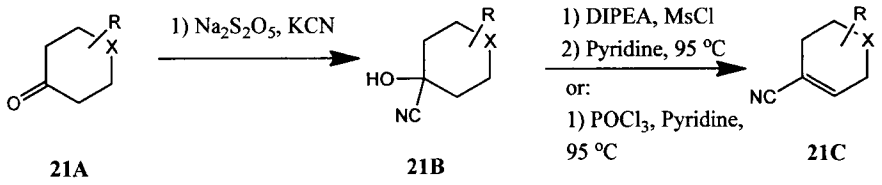
SCHEME 20



Method 21

General procedures to prepare intermediates of the instant invention are described in Scheme 21. Cyanohydrins **21B** of optionally substituted (hetero)cyclic ketones **21A** are prepared using aqueous sodium metabisulfite, followed by the addition of a suitable cyanide source, such as potassium cyanide. Hydroxyl group activation with a suitable agent, such as mesyl chloride or $POCl_3$, followed by elimination under apropriate conditions, such as refluxing pyridine, yields substituted acrylonitriles **21C** used as intermediates in the synthesis of examples of the instant invention.

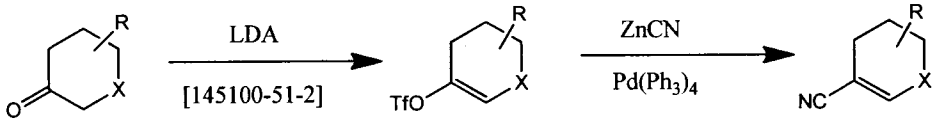
SCHEME 21



Method 22

General procedures to prepare intermediates of the instant invention are described in Scheme 22. Optionally substituted (hetero)cyclic ketones **22A** are enolized with an appropriate base, such as LDA, and reacted with a suitable triflating agent, such as N-(5-chloropyridin-2-yl)-1,1,1-trifluoro-N-(trifluoromethylsulfonyl)methanesulfonamide. The resulting vinyl triflate **22B** is reacted with a suitable palladium complex, such as tetrakis(triphenylphosphine) palladium (0), and an appropriate cyanide source, such as zinc cyanide, to afford substituted acrylonitriles **22C** used as intermediates in the synthesis of examples of the instant invention.

SCHEME 22

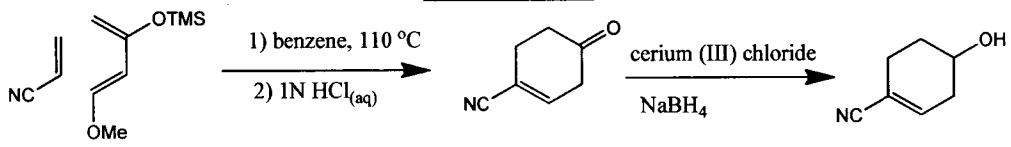


22A **22B** **22C**

Method 23

General procedures to prepare intermediates of the instant invention are described in Scheme 23. Acrylonitrile is made to under go a Diels-Alder cyclization with an appropriately substituted butadiene using standard conditions, such as refluxing benzene. The cycloaddition product is deprotected with aqueous acid, such as 1N HCl, to provide substituted cyclohexenone **23A**, which is then reacted with a suitable reductant, such as cerium (III) chloride and sodium borohydride, to afford intermediates **23B** used in the synthesis of examples of the instant invention.

SCHEME 23

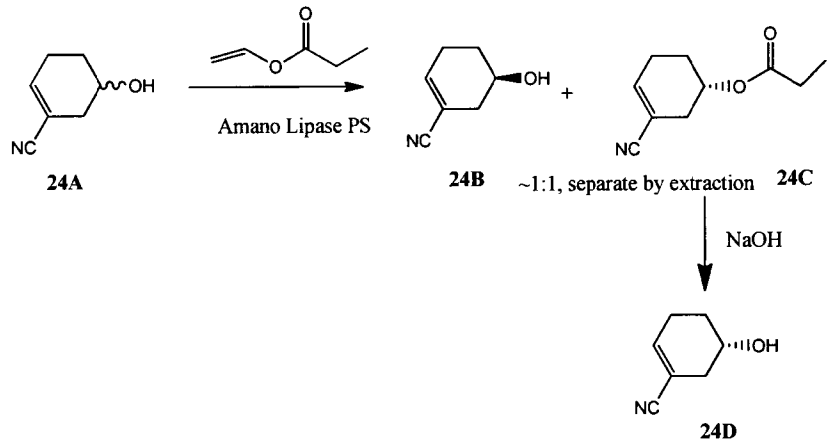


23A **23B**

Method 24

General procedures to prepare intermediates of the instant invention are described in Scheme 24. Racemic alcohol **24A** is resolved to enantiomerically enriched (R or S) **24B** and **24D**. Esterification of alcohol **24A** with a suitable ester such as vinylproprionate in the presence of a suitable enzyme such as Amano Lipase PS led to a mixture of enantiomerically enriched **24B** and ester **24C** which were separated. Saponification of **24C** using an appropriate base such as NaOH afforded intermediates **24D** used in the synthesis of examples of the instant invention.

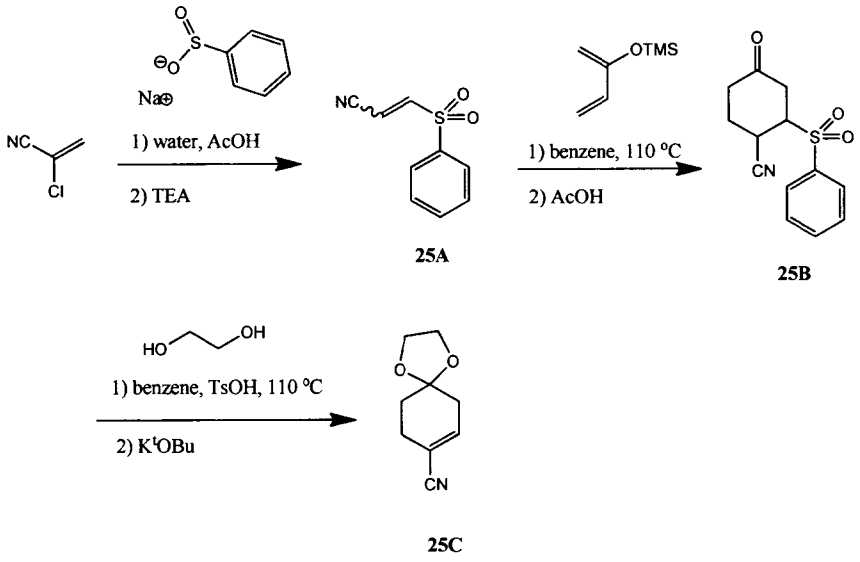
SCHEME 24



Method 25

General procedures to prepare intermediates of the instant invention are described in Scheme 25. 2-Chloroprop-2-enenitrile is reacted with benzene sulfinic acid sodium salt in aqueous acetic acid. The resulting olefin is regenerated by eliminating the chloro substituent with an appropriate base, such as TEA. The obtained acrylonitrile **25A** is made to undergo a Diels-Alder cyclization with an appropriately substituted butadiene using standard conditions, such as refluxing benzene, to yield a cyano benzosulfone substituted cyclohexanone **25B**. This substituted cyclohexanone **25B** is protected with ethylene glycol under acidic conditions, such as TsOH, in an appropriate solvent, such as benzene, at elevated temperatures, e.g. at or around 110 °C. The acetal substituted acrylonitrile **25C** is obtained after elimination of the benzosulfone with an appropriate base, such as potassium *tert*-butoxide. This synthetic sequence affords intermediates **25C** used in the synthesis of examples of the instant invention.

SCHEME 25

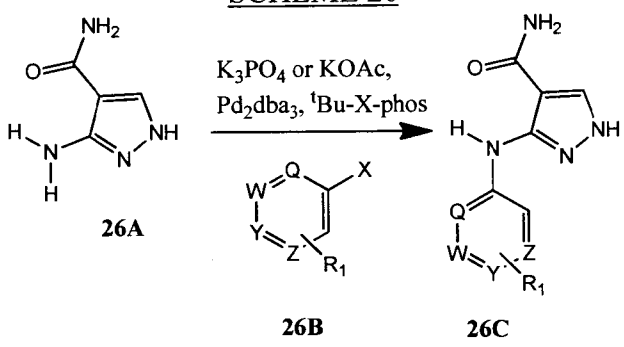


Method 26

General procedures to prepare intermediates of the instant invention are described in Scheme 26. 3-Amino pyrazole carboxamide **26A** is cross coupled to (hetero)aryl halides **26B**

using a catalytic palladium-ligand system, such as $Pd_2(dba)_3$, and Me_4-^{t}Bu-X-Phos, with a suitable base, such as K_3PO_4 or KOAc, in an appropriate solvent, such as 2-propanol, to yield pyrazole intermediates **26C**.

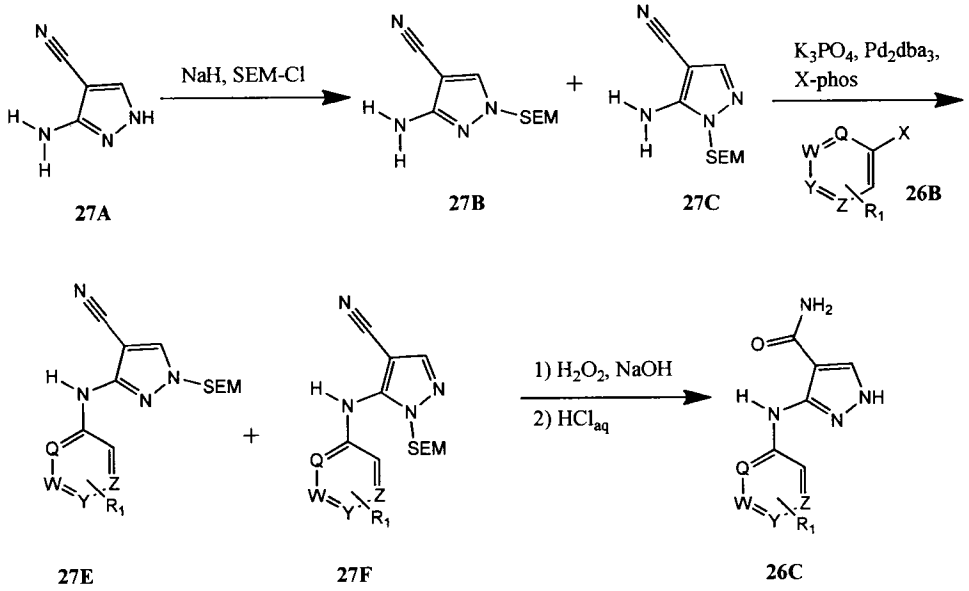
SCHEME 26



Method 27

General procedures to prepare intermediates of the instant invention are described in Scheme 27. 3-Amino-1*H*-pyrazole-4-carbonitrile **27A** is reacted with a suitable base, such as sodium hydride, and SEM-Cl to yield a mixture of 3-amino pyrazoles **27B** and **27C**, which are arylated with an appropriately substituted halogenated (hetero)aromatic **26B** using a suitable catalytic palladium-ligand system, such as $Pd_2(dba)_3$ and X-Phos, an appropriate base, such as K_3PO_4, in a suitable solvent, such as dioxane. The intermediate nitriles **27E** and **27F** are oxidized to the corresponding amides using an appropriate oxidant, such as hydrogen peroxide mixed with sodium hydroxide, and the SEM group is then removed by acid hydrolysis to yield pyrazole **26C**, an intermediate in the synthesis of examples of the instant invention.

SCHEME 27

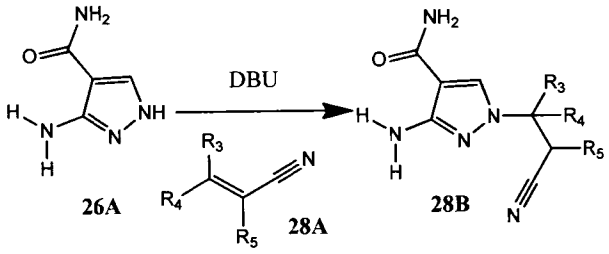


Method 28

General procedures to prepare intermediates of the instant invention are described in Scheme 28. Using an appropriate base, such as DBU, in a suitable solvent, such as MeCN,

EtOH, or *tert*-BuOH, 3-amino pyrazole carboxamide **26A** is conjugatively added to optionally substituted acrylonitriles, including but not limited to those illustrated in Schemes #18-25 to yield alkylated pyrazole carboxamide **28B**, an intermediate in the synthesis of examples of the instant invention.

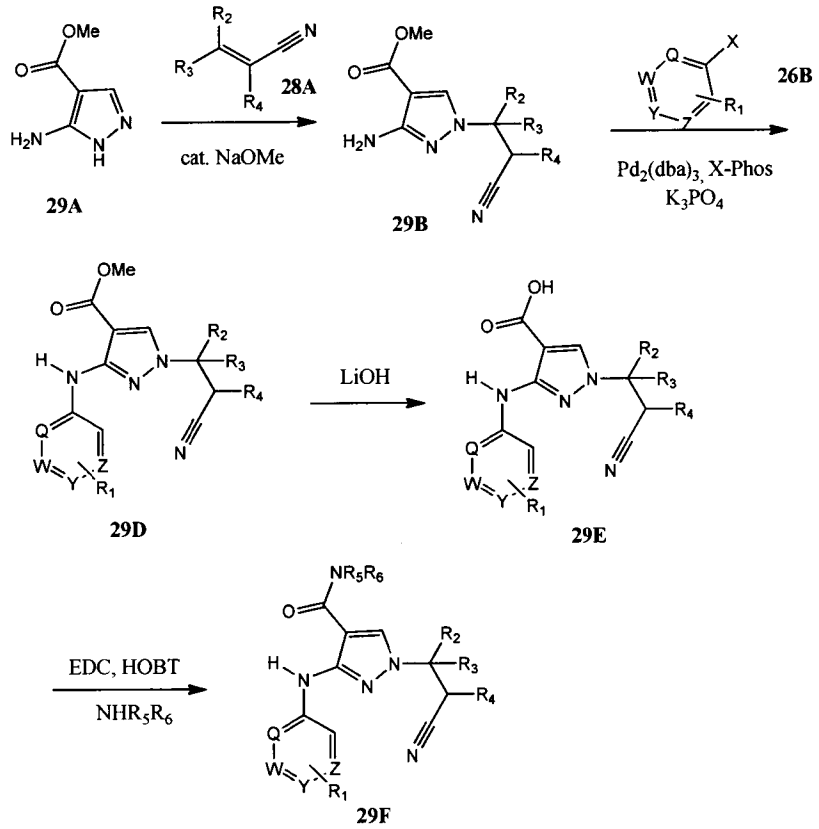
SCHEME 28



Method 29

General procedures to prepare examples of the instant invention are described in Scheme 29. Methyl 5-amino-1*H*-pyrazole-4-carboxylate **29A** is conjugatively added to substituted acrylonitriles **28A** including but not limited to those illustrated in Schemes #18-25 in the presence of a suitable base, such as catalytic sodium methoxide. The resulting intermediates **29B** are cross coupled to (hetero)aryl halides **26B** using an appropriate catalytic palladium-ligand system, such as $Pd_2(dba)_3$ and X-Phos, and an appropriate base, such as K_3PO_4. Saponification of **29D** using aqueous hydroxide, such as LiOH, followed by amide formation using standard conditions, such as EDC, HOBT, and optionally substituted primary and secondary amines yields examples **29F** of the instant invention.

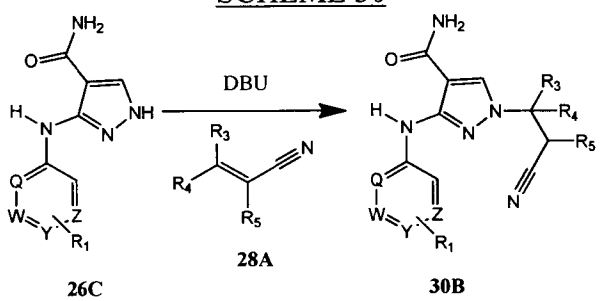
SCHEME 29



Method 30

General procedures to prepare examples of the instant invention are described in Scheme 30. Using an appropriate base, such as DBU, in a suitable solvent, such as MeCN, EtOH, or *tert*-BuOH, N-(hetero)arylated pyrazole carboxamides **26C** are conjugatively added to optionally substituted acrylonitriles **28A**, including but not limited to those illustrated in Schemes #18-25 to yield examples **30B** of the instant invention.

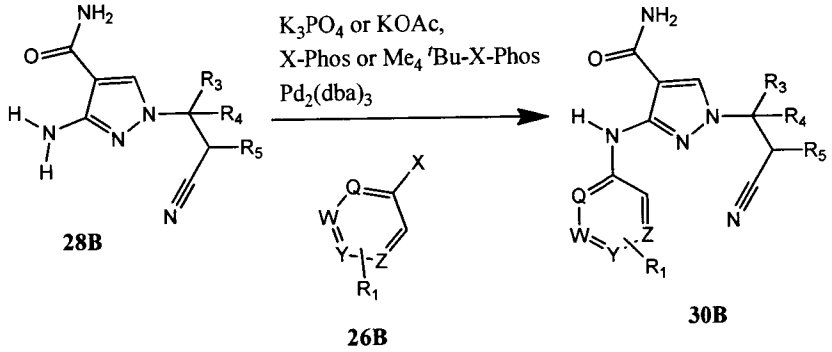
SCHEME 30



Method 31

General procedures to prepare examples of the instant invention are described in Scheme 31. Alkylated 3-amino pyrazole carboxamides **28B** are cross coupled to (hetero)aryl halides **26B** using an appropriate catalytic palladium-ligand system, such as $Pd_2(dba)_3$ and X-Phos or Me_4 ^{t}Bu-X-Phos, and a suitable base, such as K_3PO_4 or KOAc, in solvent, such as dioxane, to yield examples **30B** of the instant invention.

SCHEME 31

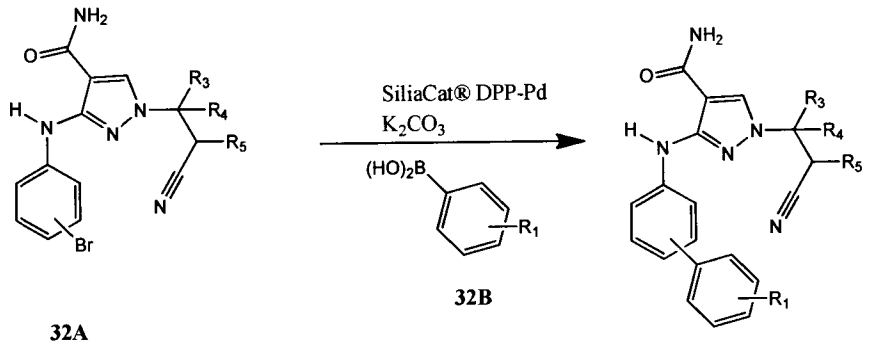


28B 26B 30B

Method 32

General procedures to prepare examples of the instant invention are described in Scheme 32. Using a solid supported palladium system, such as SiliaCat® DPP-Pd and a suitable base, such as, K_2CO_3, optionally substituted boronic acids **32B** are cross coupled to bromophenyl substituted pyrazoles **32A** to yield examples **32C** of the instant invention.

SCHEME 32

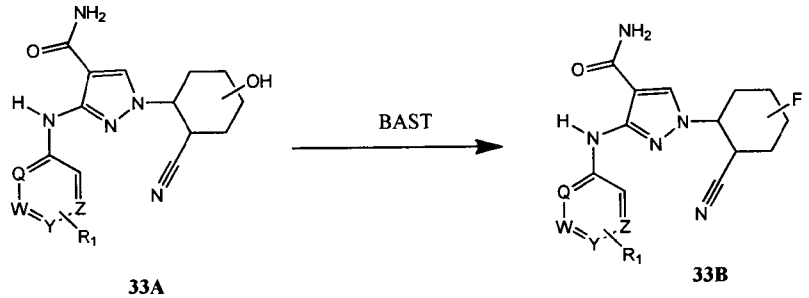


32A 32B 32C

Method 33

General procedures to prepare examples of the instant invention are described in Scheme 33. Hydroxy substituted amino pyrazole carboxamides **33A** can be fluorinated using a nucleophilic fluorine source, such as BAST, to afford examples **33B** of the instant invention.

SCHEME 33



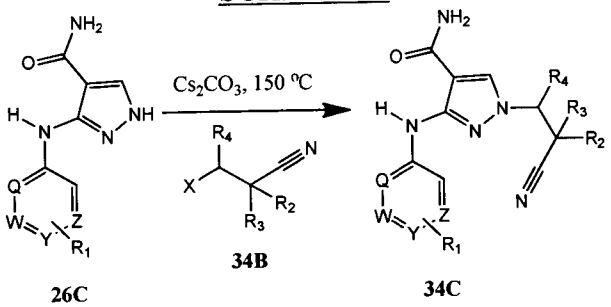
33A 33B

Method 34

General procedures to prepare examples of the instant invention are described in Scheme 34. N-(hetero)arylated pyrazole carboxamides **26C** can be alkylated with optionally

substituted alkyl halides **34B** using heat and an appropriate base, such as Cs_2CO_3, to afford examples **34C** of the instant invention.

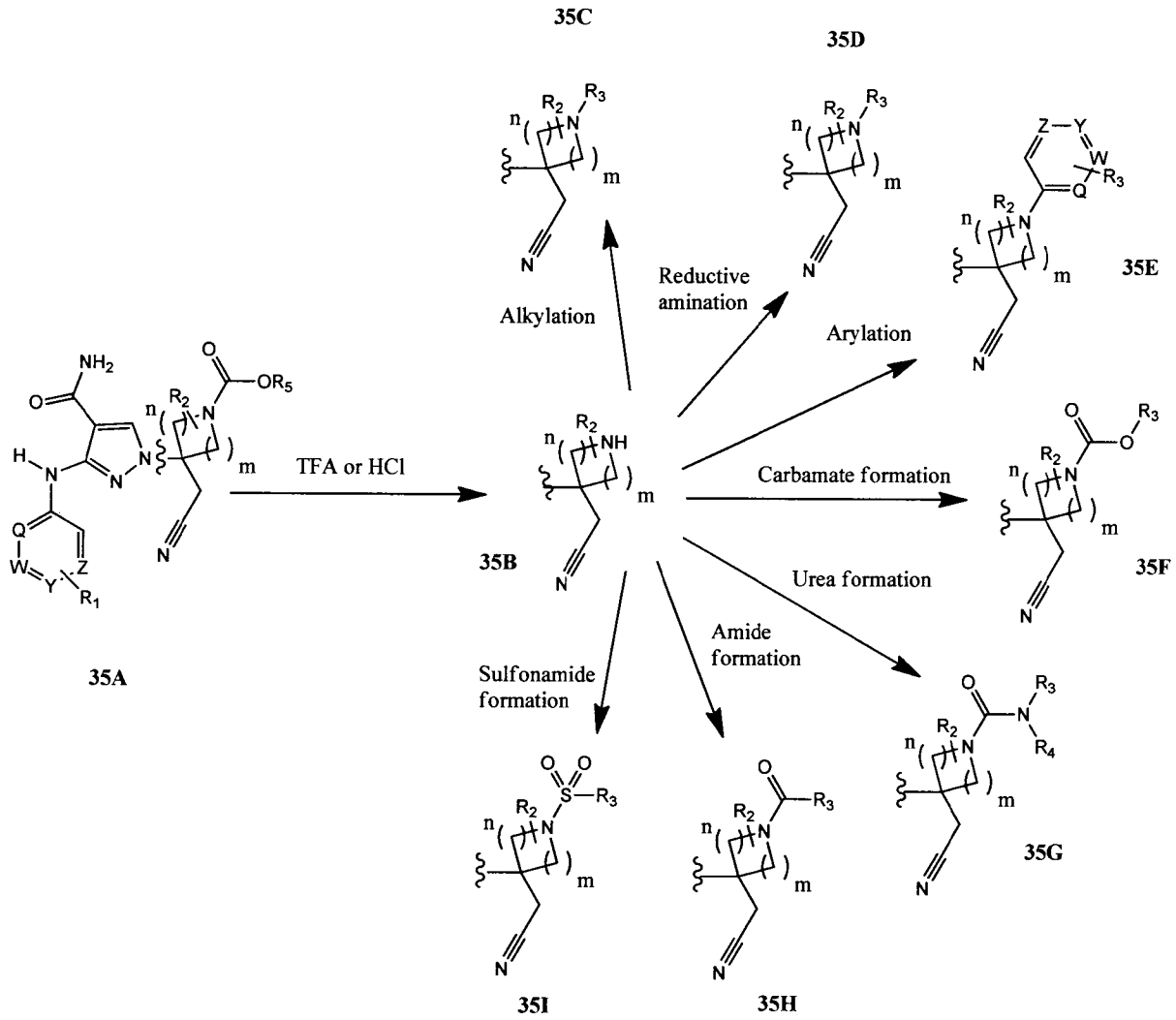
SCHEME 34



Method 35

General procedures to prepare examples of the instant invention are described in Scheme 35. Carbamate protected substituted amino pyrazole carboxamides **35A** are deprotected in the presence of acid, such as TFA or HCl, to provide amino intermediates **35B** which are further derivatized using standard conditions known by those skilled in the art to yield examples of the instant invention. Examples include but are not limited to alkylated **35C**, reductively aminated **35D**, and arylated **35E** derivatives, as well as carbamates **35F**, ureas **35G**, amides **35H**, and sulfonamides **35I**.

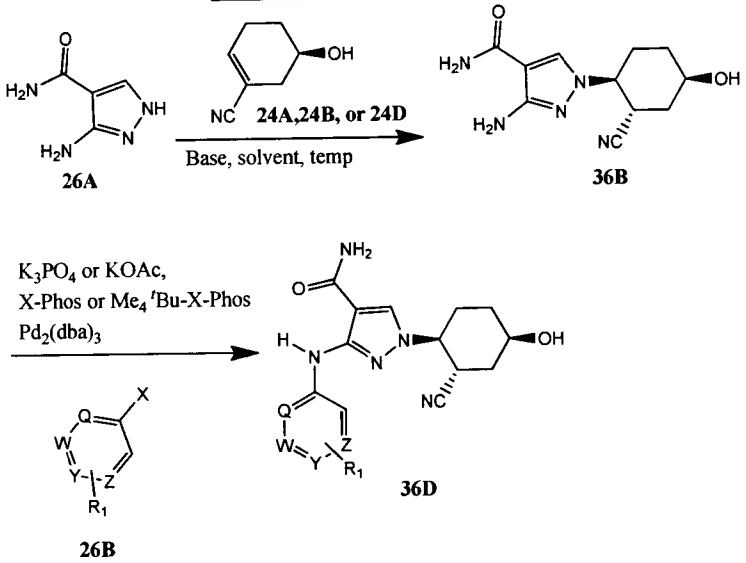
SCHEME 35



Method 36: Alcohol A

General procedures to prepare examples of the instant invention are described in Scheme 36. Using an appropriate base, such as DBU, in a suitable solvent, such as MeCN, EtOH, or *tert*-BuOH, N-(hetero)arylated pyrazole carboxamides **26A** are conjugatively added to acrylonitrile **24A, 24B,** or **24D** to afford examples **36B.** Alkylated 3-amino pyrazole carboxamides **36B** are cross coupled to (hetero)aryl halides **26B** using an appropriate catalytic palladium-ligand system, such as $Pd_2(dba)_3$ and X-Phos or Me_4 ^{t}Bu-X-Phos, and a suitable base, such as K_3PO_4 or KOAc, in solvent, such as dioxane, to yield examples **36D** (which are either racemic if alcohol **24A** was used or chiral if alcohols **24B** or **24D** were used) of the instant invention.

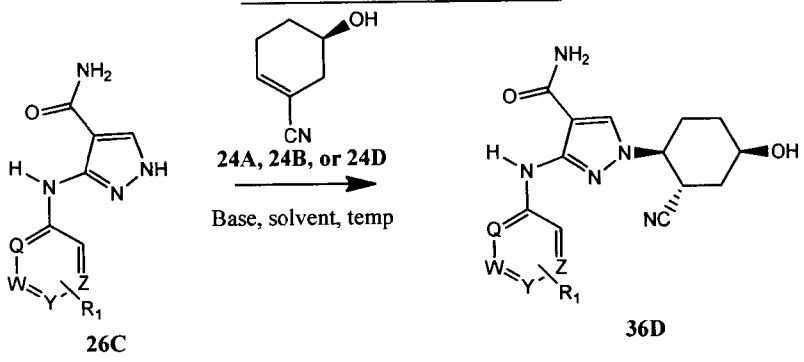
SCHEME 36: Alcohol A



Method 37: Alcohol B

General procedures to prepare examples of the instant invention are described in Scheme 37. Using an appropriate base, such as DBU, in a suitable solvent, such as MeCN, EtOH, or *tert*-BuOH, N-(hetero)arylated pyrazole carboxamides **26C** are conjugatively added to acrylonitrile **24A, 24B,** or **24D** to afford examples **36D** (which are either racemic if alcohol **24A** was used or chiral if alcohols **24B** or **24D** were used) of the instant invention.

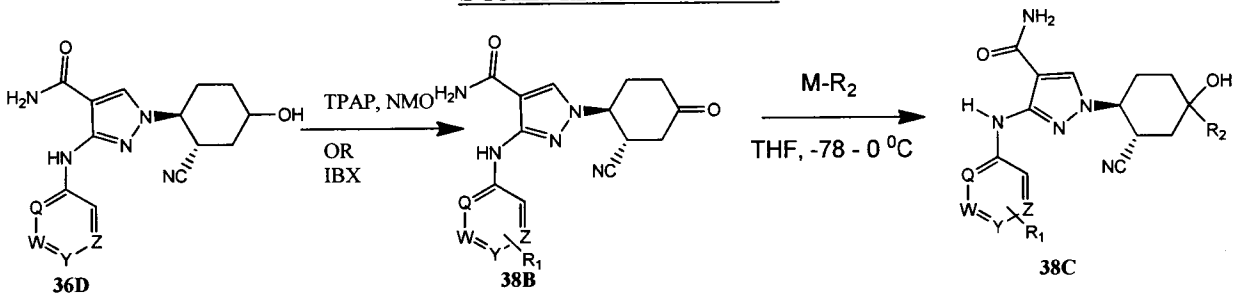
SCHEME 37: Alcohol B



Method 38: Alcohol C

General procedures to prepare examples of the instant invention are described in Scheme 38. Hydroxylated cyclohexyl pyrazole carboxamides **36D** can be oxidized with an appropriate oxidant, such as TPAP/NMO or IBX, to afford ketone **38B** which is then reacted with alkyl-metal reagents, sucg as Grignard reagents, in an appropriate solvent, such as THF, at an appropriate temperature, for example between -78 and 0 °C, to afford examples **38C** (which are either racemic if alcohol **24A** was used or chiral if alcohols **24B** or **24D** were used) of the instant invention.

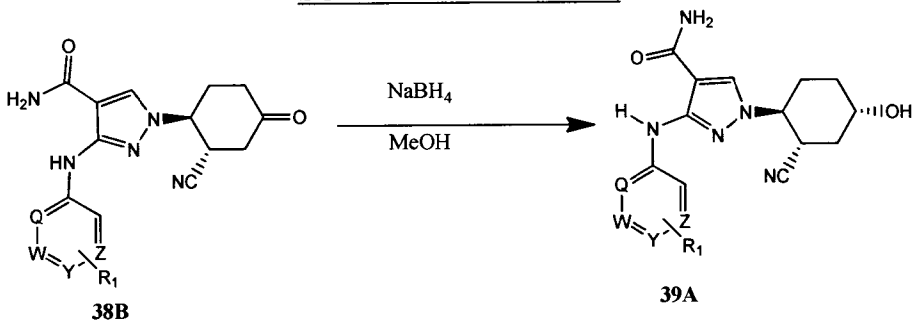
SCHEME 38: Alcohol C



Method 39: Alcohol D

General procedures to prepare examples of the instant invention are described in Scheme 39. Ketone **38B** is reduced to alcohol **39A** with a suitable reducing agent, such as $NaBH_4$, in a suitable solvent such as methanol to afford examples **39A** of the instant invention.

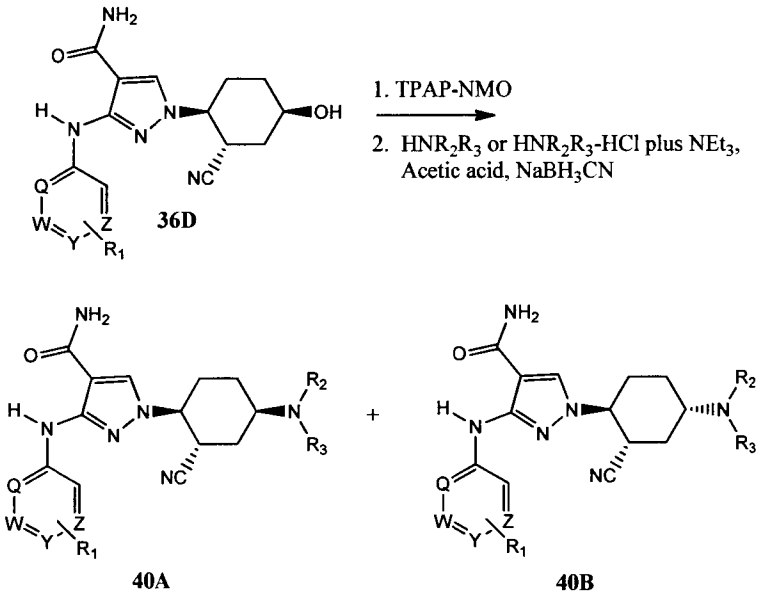
SCHEME 39: Alcohol D



Method 40

General procedures to prepare examples of the instant invention are described in Scheme 40. Hydroxylated cyclohexyl pyrazole carboxamides **36D** can be oxidized with an appropriate oxidant, such as TPAP and NMO, and then reductively aminated using standard conditions, such as AcOH, $NaCNBH_3$ and optionally substituted primary and secondary amines, to afford examples **40A** and **40B** of the instant invention.

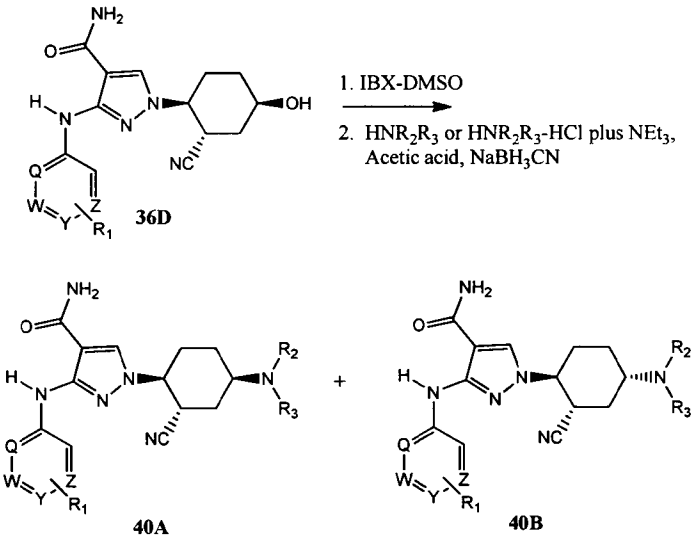
SCHEME 40



Method 41

General procedures to prepare examples of the instant invention are described in Scheme 41. Hydroxylated cyclohexyl pyrazole carboxamides **36D** can be oxidized with an appropriate oxidant, such as IBX, and then reductively aminated using standard conditions, such as AcOH, $NaCNBH_3$, and optionally substituted primary and secondary amines, to afford examples **40A** and **40B** of the instant invention.

SCHEME 41

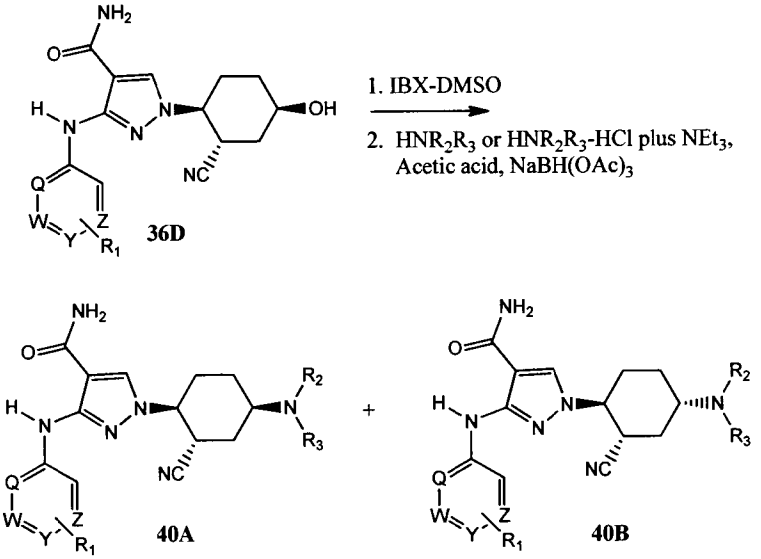


Method 42

General procedures to prepare examples of the instant invention are described in Scheme 42. Hydroxylated cyclohexyl pyrazole carboxamides **36D** can be oxidized with an appropriate oxidant, such as IBX, and then reductively aminated using standard conditions, such

as AcOH, $NaBH(OAc)_3$, and optionally substituted primary and secondary amines, to afford examples **40A** and **40B** of the instant invention.

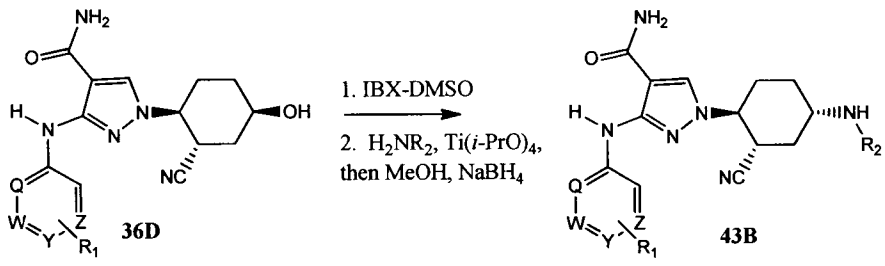
SCHEME 42



Method 43

General procedures to prepare examples of the instant invention are described in Scheme 43. Hydroxylated cyclohexyl pyrazole carboxamides **36D** can be oxidized with an appropriate oxidant, such as IBX, and then reductively aminated using a 2-step protocol. For example, the ketone is treated with a primary amine and a Lewis acid, such as $Ti(i\text{-}PrO)_4$ followed by rection with a metal hydride such as $NaBH_4$ in a solvent such as methanol to afford example **43B** of the instant invention.

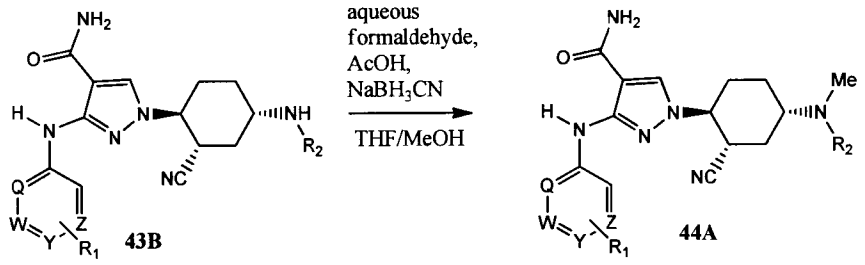
SCHEME 43



Method 44

General procedures to prepare examples of the instant invention are described in Scheme 44. Secondary amines **43B** were subjected to reductive amination conditions such as AcOH, aqueous formaldehyde, a reducing agent such as $NaCNBH_3$, and in a suitable solvent mixture such as THF/methanol to afford examples **44A** of the instant invention.

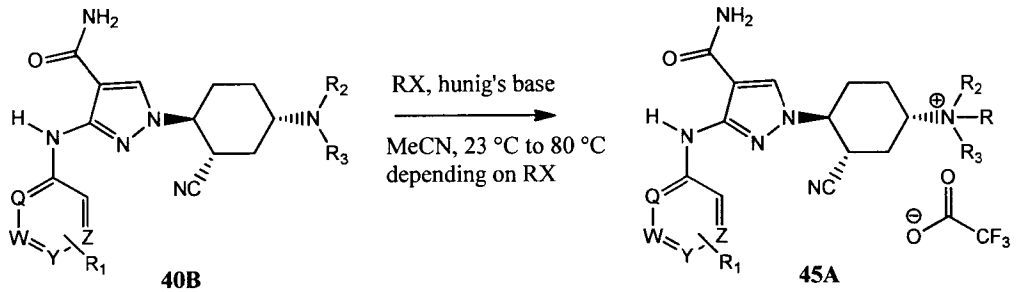
SCHEME 44



Method 45

General procedures to prepare examples of the instant invention are described in Scheme 45. Tertiaryamino-cyclohexyl pyrazole carboxamides **40B** reacted with alkyl halides, such as but not limited to methyl iodide, in a suitable solvent such as acetonitrile, at an appropriate temperature, such as between 23 and 80 °C, to afford quaternary amine derivatives **45A** of the instant invention.

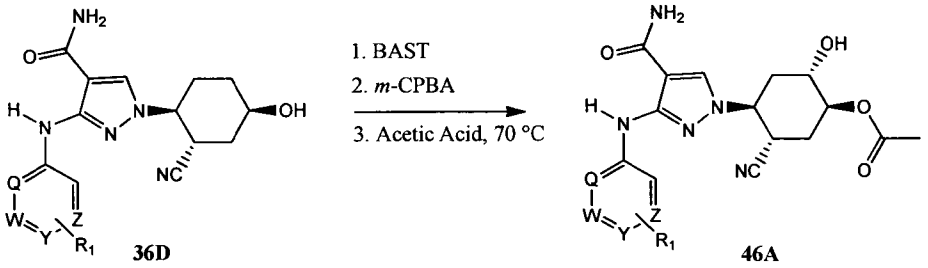
SCHEME 45



Method 46

General procedures to prepare examples of the instant invention are described in Scheme 46. Hydroxycyclohexyl pyrazole carboxamides **36D** reacted with BAST to afford a regioselective dehydration to a cyclohexene derivative which reacted with a peroxide, such as *m*-CPBA, to afford an epoxide which reacted with acetic acid to afford **46A** of the instant invention.

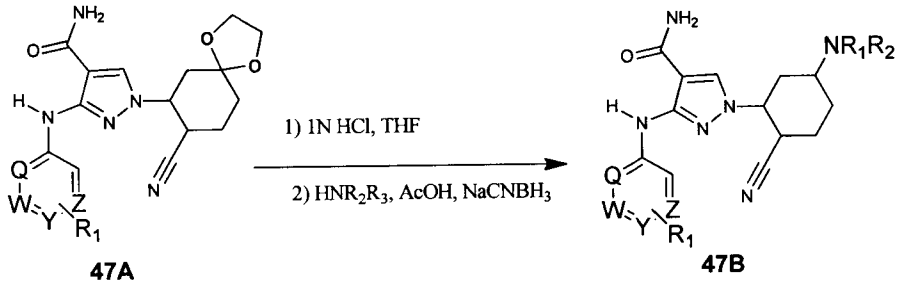
SCHEME 46



Method 47

General procedures to prepare examples of the instant invention are described in Scheme 47. Ketal-cyclohexyl pyrazole carboxamides **47A** reacted under aqueous acid conditions, such as aqueous HCl in THF at a temperature between 23 and 80 °C afforded the ketone derivative, which was reductively aminated using standard conditions, such as AcOH, $NaBH(OAc)_3$, and optionally substituted primary and secondary amines, to afford examples **47B** of the instant invention.

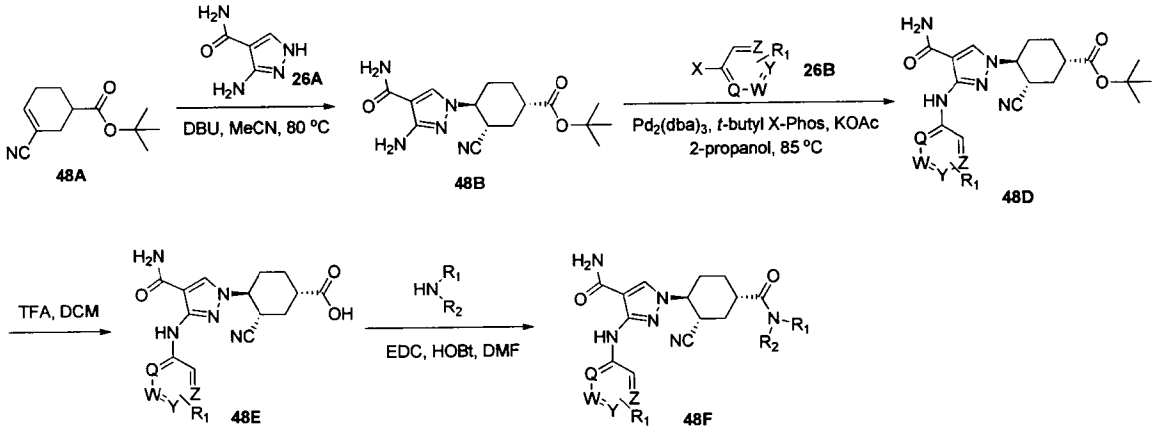
SCHEME 47



Method 48

General procedures to prepare examples of the instant invention are described in Scheme 48. Using an appropriate base, such as DBU, in a suitable solvent, such as MeCN, pyrazole carboxamide **26A** is conjugatively added to acrylonitrile **48A** to afford intermediate **48B.** Alkylated 3-amino pyrazole carboxamides **48B** are cross coupled to (hetero)aryl halides **26B** using an appropriate catalytic palladium-ligand system, such as $Pd_2(dba)_3$ and X-Phos or Me_4 ^{t}Bu-X-Phos, and a suitable base, such as KOAc, in solvent, such as 2-propanol, to yield **48D.** Carboxylic acid **48E** is formed under acidic conditions such as TFA in a suitable solvent such as DCM which is subsequently reacted with suitably substituted primary and secondary amines under standard amide coupling conditions such as EDC/HOBT to afford examples **48F** of the instant invention.

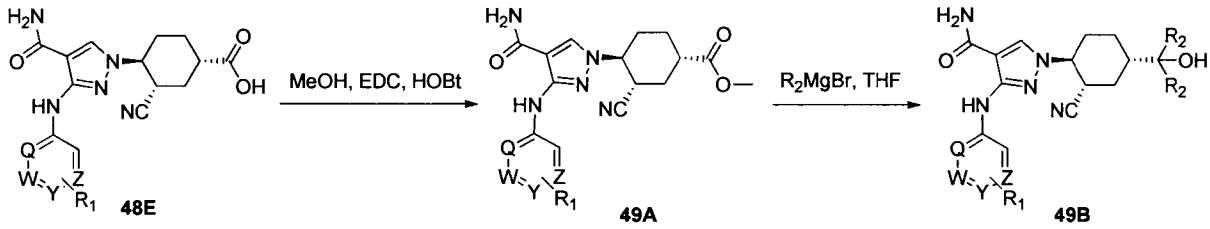
SCHEME 48



Method 49

General procedures to prepare examples of the instant invention are described in Scheme 49. Carboxylic acid derivatives **48E** can be reacted under standard coupling conditions such as EDC/HOBT in an alcoholic solvent such as methanol to afford methyl ester **49A** which is further reacted with alkyl Grignard reagents in a suitable solvent such as THF to afford alcohol derivatives **49B** of the instant invention.

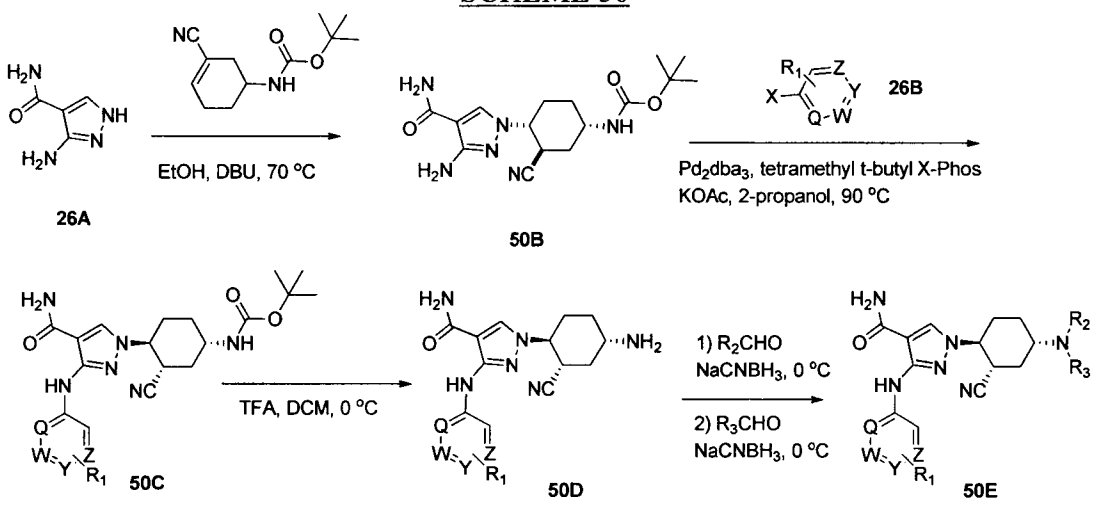
SCHEME 49



Method 50

General procedures to prepare examples of the instant invention are described in Scheme 50. Using an appropriate base, such as DBU, in a suitable solvent, such as ethanol, pyrazole carboxamide **26A** is conjugatively added to acrylonitrile **50A** to afford intermediate **50B.** Alkylated 3-amino pyrazole carboxamides **50B** are cross coupled to (hetero)aryl halides **26B** using an appropriate catalytic palladium-ligand system, such as $Pd_2(dba)_3$ and X-Phos or Me_4 ^{t}Bu-X-Phos, and a suitable base, such as KOAc, in solvent, such as 2-propanol, to yield **50C.** Under acidic conditions such as TFA in a suitable solvent such as DCM, amine derivatives **50D** were formed which were sequentially reductively aminated with optionally substituted aldehydes using standard conditions, such as AcOH, $NaBH(OAc)_3$ which afforded examples **50E** of the instant invention.

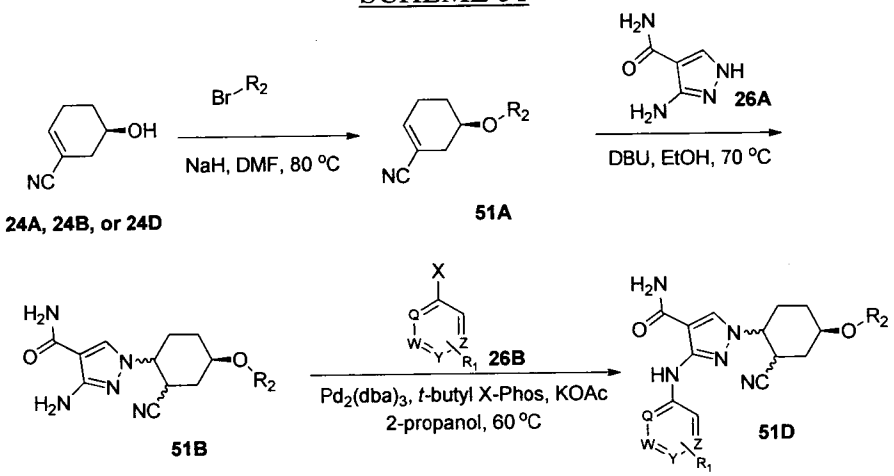
SCHEME 50



Method 51

General procedures to prepare examples of the instant invention are described in Scheme 51. Hydroxylated cyclohexene **24A** is reacted with an appropriate base such as sodium hydride, in a suitable solvent such as DMF, and treated with optionally substituted alkyl halides to afford ethers **51A**. Using an appropriate base, such as DBU, in a suitable solvent, such as ethanol, pyrazole carboxamide **26A** is conjugatively added to acrylonitrile **51A** to afford intermediate **51B.** Alkylated 3-amino pyrazole carboxamides **51B** are cross coupled to (hetero)aryl halides **26B** using an appropriate catalytic palladium-ligand system, such as $Pd_2(dba)_3$ and X-Phos or Me_4 ^{t}Bu-X-Phos, and a suitable base, such as KOAc, in solvent, such as 2-propanol, to yield examples **51D** of the instant invention.

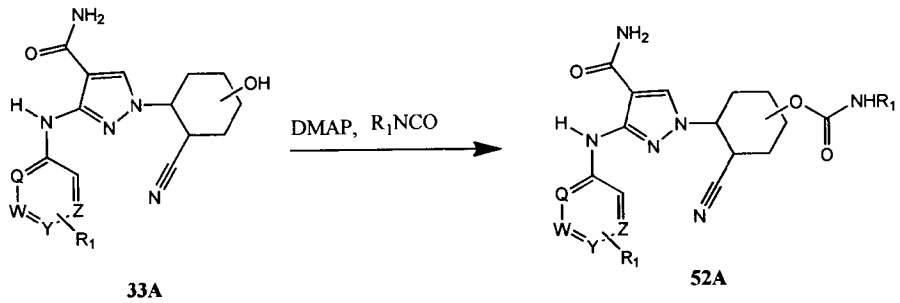
SCHEME 51



Method 52

General procedures to prepare examples of the instant invention are described in Scheme 52. Hydroxylated cyclohexyl pyrazole carboxamides **33A** can be reacted with optionally substituted isocyanates and DMAP to afford carbamate derivatives **52A** of the instant invention.

SCHEME 52

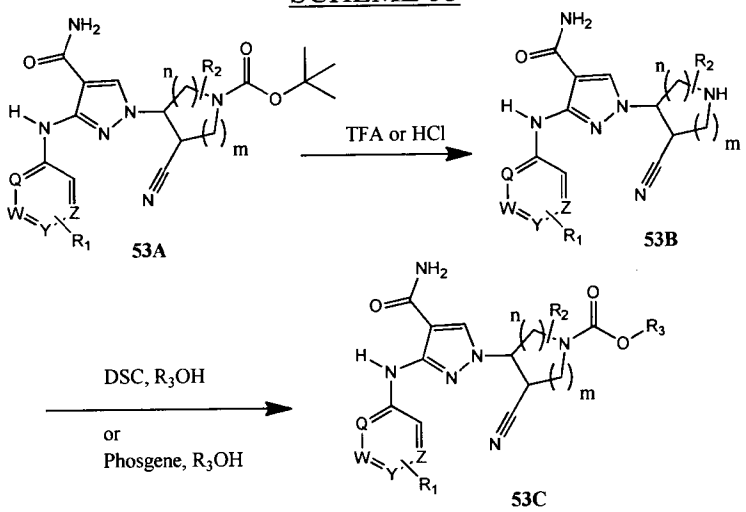


Method 53

General procedures to prepare examples of the instant invention are described in Scheme 53. Optionally substituted, carbamate protected pyrazole carboxamides **53A** are deprotected in the presence of acid, such as TFA or HCl, and then reacted with optionally

substituted alcohols in the presence of a doubly activated carbonyl group, such as DSC or phosgene, to afford carbamate derivatives **53C** of the instant invention.

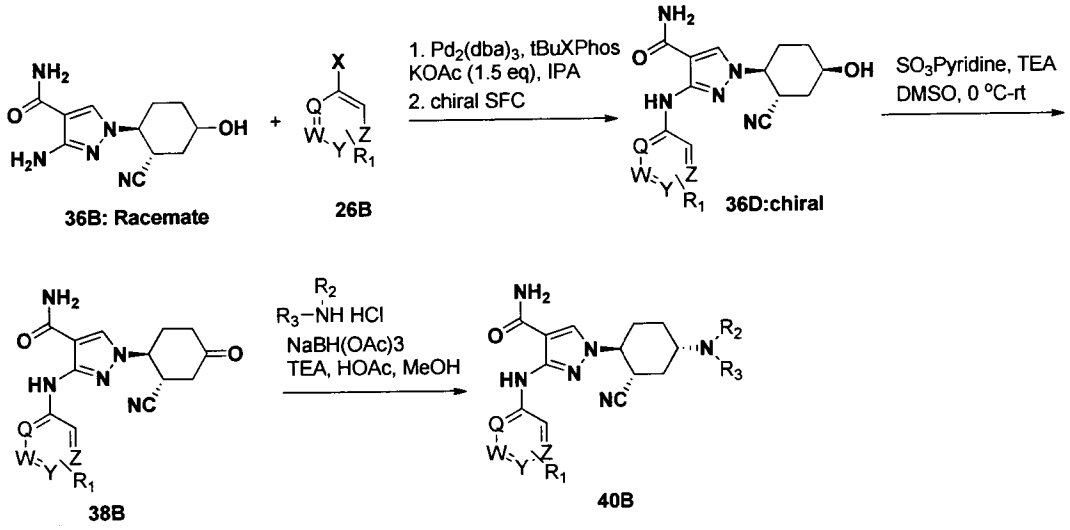
SCHEME 53



Method 54

General procedures to prepare examples of the instant invention are described in Scheme 54. Alkylated 3-amino pyrazole carboxamides **36B** are cross coupled to (hetero)aryl halides **26B** using an appropriate catalytic palladium-ligand system, such as $Pd_2(dba)_3$ and X-Phos or Me_4 ^{t}Bu-X-Phos, and a suitable base, such as KOAc, in a solvent such as isopropanol. The racemic derivative is purified on a chiral stationary phase column to yield enantioenriched examples **36D**. Hydroxylated cyclohexyl pyrazole carboxamides **36D** can be oxidized with an appropriate oxidant, such as a Swern method, and then reductively aminated using standard conditions, such as AcOH, $NaBH(OAc)_3$, and optionally substituted primary and secondary amines, to afford examples **40B** of the instant invention.

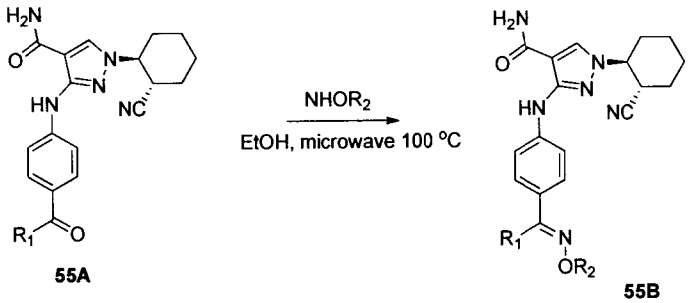
SCHEME 54



Method 55

General procedures to prepare examples of the instant invention are described in Scheme 55. Substituted amino pyrazole 55A can be aminated with optionally substituted hydroxylamines with heating in a suitable solvent, such as ethanol to afford examples 55B of the instant invention.

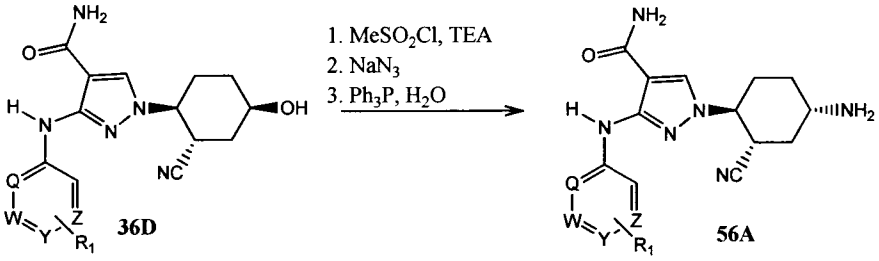
SCHEME 55



Method 56

General procedures to prepare examples of the instant invention are described in Scheme 56. Hydroxylated cyclohexyl pyrazole carboxamides **36D** can be activated with methane sulfonylchloride in the presence of a base such as TEA. The mesylate intermediate can be displaced with a metal-azide, such as sodium azide, which can be subsequently reduced, for example with triphenylphosphine in an appropriate solvent such as aqueous THF, to afford examples **56A** of the instant invention.

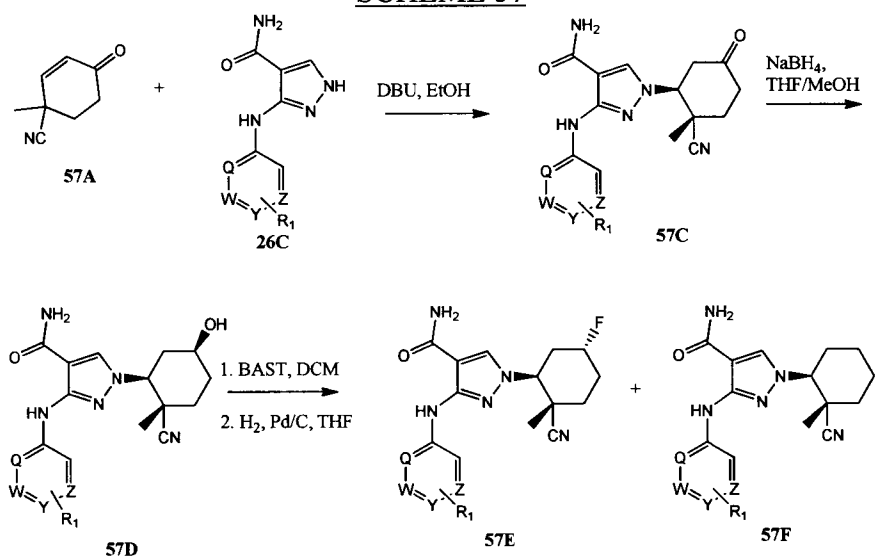
SCHEME 56



Method 57

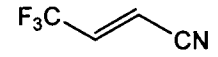
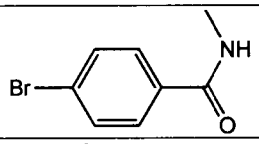
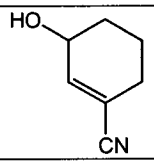
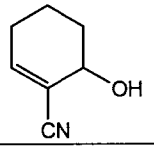
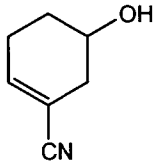
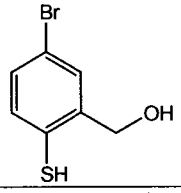
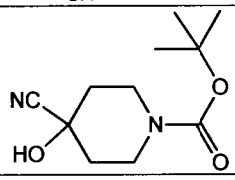
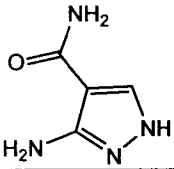
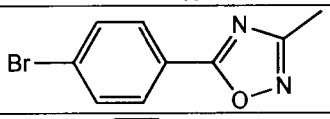
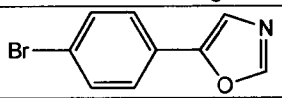
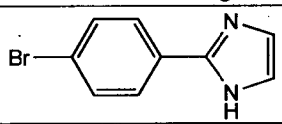
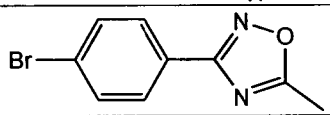
General procedures to prepare examples of the instant invention are described in Scheme 57. Using an appropriate base, such as DBU, in a suitable solvent, such as ethanol, pyrazole carboxamide **26C** is conjugatively added to acrylonitrile **57A** to afford example **57C.** Ketone **57C** is subsequently reduced to alcohol **57D** with a suitable reducing agent, such as $NaBH_4$, in a suitable solvent mixture such as THF/methanol. Treament of **57D** with a nucleophilic fluoride source, such as BAST, followed by hydrogenation using a catalyst such as paladium on carbon to reduce an olefin byproduct, afforded **57E** and **57F** of the instant invention.

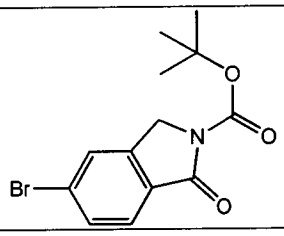
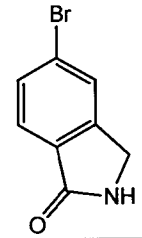
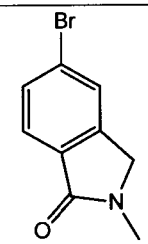
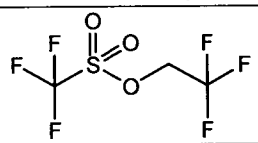
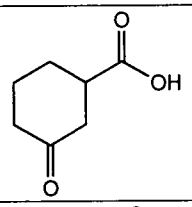
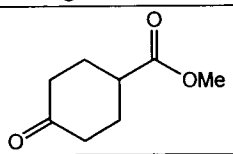
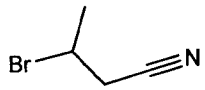
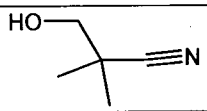
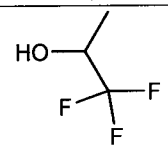
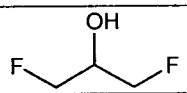
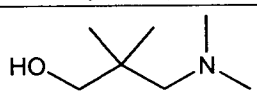
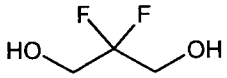
SCHEME 57



COMMERCIALLY AVAILABLE / PREVIOUSLY DESCRIBED MATERIALS

The following table lists commercial sources, and previously disclosed synthetic routes for chemical materials employed in the synthesis of intermediates, and Examples of the instant invention. The list is not intended to be exhaustive, exclusive, or limiting in any way.

Structure	Compound Name	Vendor
	4,4,4-trifluorobut-2-enenitrile	Oakwood
	4-bromo-*N*-methylbenzamide	Combi Blocks, Inc.
	3-hydroxycyclohex-1-ene-1-carbonitrile	J. Org. Chem. 2001, *66*, 2171-2174.
	6-hydroxycyclohex-1-ene-1-carbonitrile	Tetrahedron Letters 1986, *27*, 1577-1578.
	5-hydroxycyclohex-1-ene-1-carbonitrile	Canadian Journal of Chemistry 1984, *62*, 1093-1098.
	(5-bromo-2-mercaptophenyl)methanol	Biogene Organics, Inc.
	*tert*-butyl 4-cyano-4-hydroxypiperidine-1-carboxylate	Sinova, Inc.
	3-amino-1*H*-pyrazole-4-carboxamide	Enamine
	5-(4-bromophenyl)-3-methyl-1,2,4-oxadiazole	Maybridge
	5-(4-bromophenyl)-1,3-oxazole	Maybridge
	2-(4-bromophenyl)-1*H*-imidazole	J&W Pharmlab LLC
	3-(4-bromophenyl)-5-methyl-1,2,4-oxadiazole	Maybridge

	*tert*-butyl 5-bromo-1-oxo-1,3-dihydro-2*H*-isoindole-2-carboxylate	Ontario Chemical, Inc.
	5-bromo-2,3-dihydro-1*H*-isoindol-1-one	Atomole Scientific Co, ltd.
	5-bromo-2-methyl-2,3-dihydro-1*H*-isoindol-1-one	J&W Pharmlab LLC
	2,2,2-trifluoroethyl trifluoromethanesulfonate	Matrix Scientific
	3-oxocyclohexanecarboxylic acid	Sigma Aldrich
	methyl 4-oxocyclohexanecarboxylate	Astatech Inc
	3-bromobutyronitrile	TCI America
	3-hydroxy-2,2-dimethylpropanenitrile	Matrix Scientific
	1,1,1-trifluoro-2-propanol	Sigma Aldrich
	1,3-difluoro-2-propanol	Sigma Aldrich
	3-dimethylamino-2,2-dimethyl-1-propanol	TCI America
	2,2-difluoropropane-1,3-diol	Chemstep

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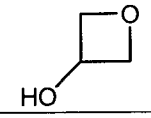
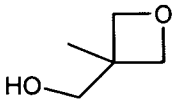
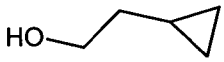
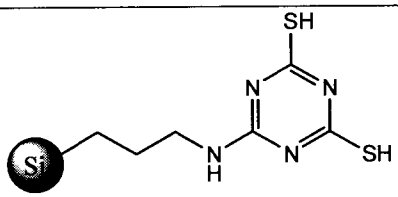
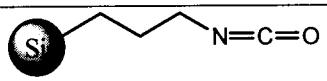
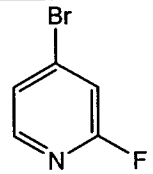
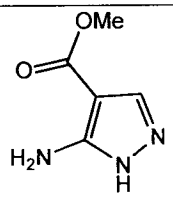
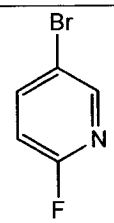
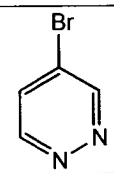
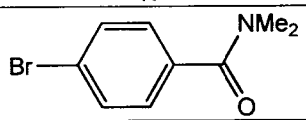
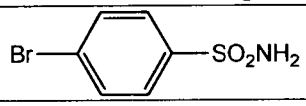
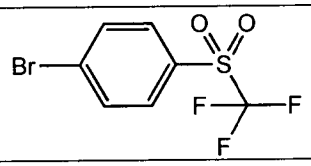
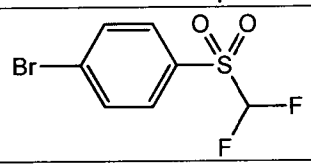
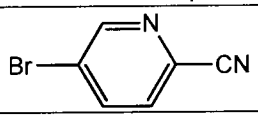
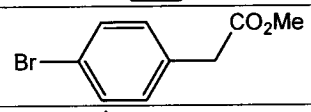
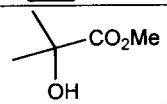
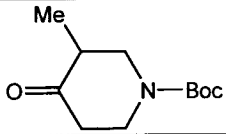
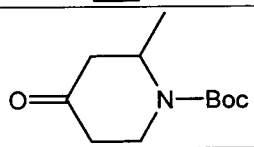
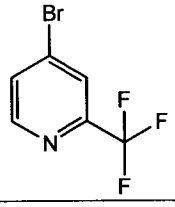
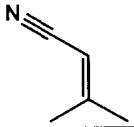
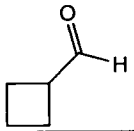
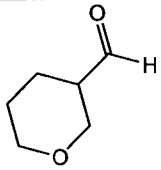
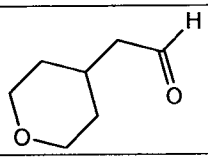
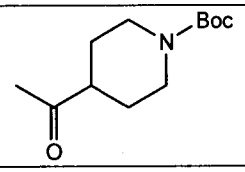
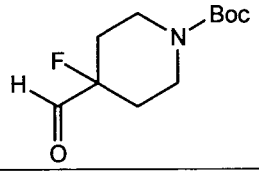
	oxetan-3-ol	Sigma Aldrich
	(3-methyloxetan-3-yl)methanol	Sigma Aldrich
	2-cyclopropylethanol	Sigma Aldrich
	Silica supported Dimercaptotriazine (Si-DMT)	Silicycle Inc.
	Silica supported Isocyanate	Silicycle Inc.
	4-bromo-2-fluoropyridine	Synthonix
	methyl 5-amino-1*H*-pyrazole-4-carboxylate	Chembridge Corporation
	5-bromo-2-fluoropyridine	Matrix Scientific
	4-bromopyridazine	Fisher Scientific
	4-bromo-*N*,*N*-dimethylbenzamide	Chembridge Corporation
	4-bromobenzenesulfonamide	Sigma Aldrich

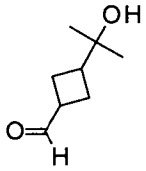
	1-bromo-4-[(trifluoromethyl)sulfonyl]benzene	Sunshine Chemlab. Inc
	1-bromo-4-[(difluoromethyl)sulfonyl]benzene	WXAT
	5-bromopyridine-2-carbonitrile	Sigma Aldrich
	methyl (4-bromophenyl)acetate	Toyobo Co., Ltd.
	methyl 2-hydroxy-2-methylpropanoate	Sigma Aldrich
	*tert*-butyl 3-methyl-4-oxopiperidine-1-carboxylate	Small Molecules Inc.
	*tert*-butyl 2-methyl-4-oxopiperidine-1-carboxylate	Small Molecules Inc.
	4-bromo-2-(trifluoromethyl)pyridine	CombiPhos Catalysts, Inc.
	3-methylbut-2-enenitrile	BePharm Ltd.
	cyclobutanecarbaldehyde	Beta Pharma Inc
	tetrahydro-2*H*-pyran-3-carbaldehyde	J&W Pharmlab LLC
	tetrahydro-2*H*-pyran-4-ylacetaldehyde	Maybridge

	*tert*-butyl 4-acetylpiperidine-1-carboxylate	Syntech Development Company
	*tert*-butyl 4-fluoro-4-formylpiperidine-1-carboxylate	Ark Pharm, Inc.

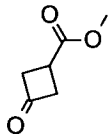
INTERMEDIATES

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 f the instant invention in any way.

Intermediate #1

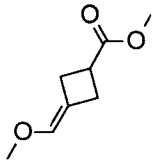


3-(2-Hydroxypropan-2-yl)cyclobutanecarbaldehyde



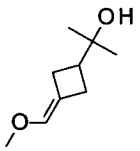
Step A: **Methyl 3-oxocyclobutanecarboxylate**

3-Oxocyclobutanecarboxylic acid 1 (350 g, 3.06 mol), methanol (190 mL, 4.69 mol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (885 g, 4.69 mol), 4-dimethylaminopyridine (37 g, 0.30 mol) and dichloromethane (6 L) were stirred at ambient temperature for 24 hours. After the completion of the reaction, it was taken in a separating funnel and washed with 1.5 N HCl solution (1 L), water (2 L x 2) and brine (1 L x 2). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was taken to the next step without further purification. ^1H NMR (300 MHz, $CDCl_3$): δ 3.23-3.25 (m, 2H), 3.27-3.32 (m, 2H), 3.33-3.42 (m, 1H), 3.76 (s, 3H). GC-MS: $[M]^+$ *m/z* = 128.



Step B: **Methyl 3-(methoxymethylidene)cyclobutanecarboxylate**

To a suspension of methoxymethyltriphenylphosphonium chloride (1350 g, 3.90 mol) in anhydrous benzene (12 L), a solution of sodium *tert*-pentoxide (435 g, 3.90 mol) in anhydrous benzene (4 L) was added slowly under nitrogen atmosphere. The resulting red solution was stirred for 15 minutes at ambient temperature. Then, a solution of methyl 3-oxocyclobutanecarboxylate (250 g, 1.95 mol) in anhydrous benzene (1 L) was added slowly and the reaction mixture was heated at 70 °C for 2 hours. Saturated aqueous ammonium chloride (~ 4 L) was added to the reaction mixture and extracted with diethyl ether (5 L). The organic layer was washed with water (5 L x 2), brine (5 L), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (mesh 60-120; eluent: 10% diethyl ether in hexane) to afford the title compound as a pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.89-2.92 (m, 2H), 2.96-3.0 (m, 2H), 3.14-3.17 (m, 1H), 3.56 (s, 3H), 3.70 (s, 3H), 5.81-5.83 (m, 1H). GC-MS: $[M]^+$ *m/z* = 156.



Step C: **2-[3-(Methoxymethylidene)cyclobutyl]propan-2-ol**

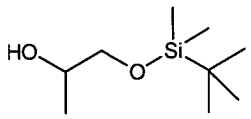
Methylmagnesium chloride (3 M in THF, 500 mL, 0.736 mol) was slowly added to a solution of methyl 3-(methoxymethylidene)cyclobutanecarboxylate (92 g 0.59 mol) in anhydrous THF (1 L) at 0 °C over a period of 0.5 hours and stirred at ambient temperature for 2 hours. It was cooled to 0 °C and saturated aqueous ammonium chloride (200 mL) was added very slowly. Then the reaction mixture was extracted with EtOAc(250 mL x 2) and the combined organic layer was washed with water (250 mL x 2), brine (500 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (mesh 60-120; eluent: 10% EtOAc/hexane) to afford the title compound as pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (s, 6H), 2.40-2.44 (m, 1H), 2.54-2.69 (m, 4H), 3.56 (s, 3H), 5.80-5.82 (m, 1H). GC-MS: $[M]^+$ *m/z* = 156.

Step D: **3-(2-Hydroxypropan-2-yl)cyclobutanecarbaldehyde**

Oxalic acid dihydrate (68 g, 0.54 mol) was added to a solution of 2-[3-(methoxymethylidene)cyclobutyl]propan-2-ol (70 g, 0.45 mol) in THF:H_2O (1:1, 700 mL) at 0 °C and stirred at ambient temperature for 1 hour. Then, 10 % aqueous $NaHCO_3$ solution was added to the reaction mixture and extracted with EtOAc(500 mL x 4). The combined organic layer was then washed with water (200 mL x 2), brine (200 mL) dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a pale yellow liquid (mixture of *cis* and *trans* isomers). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of *cis* and *trans*): δ 1.09-1.11 (2 s, 6H), 2.07-2.26 (m, 4H), 2.31-2.39 (m, 1H), 2.95-2.99 (m, 1H), 9.75 & 9.84 (2 s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, mixture of *cis* and *trans*): δ 21.8, 26.1, 39.4, 40.7, 41.8, 70.3, 202.6. ^{1}H NMR

(400 MHz, DMSO-d_6, mixture of *cis* and *trans*): δ 0.96 (s, 3H), 0.98 (s, 3H), 1.88-2.29 (m, 5H), 2.87-2.92 (m, 1H), 4.13 & 4.21 (2 s, 1H), 9.56 & 9.74 (2 s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6, mixture of *cis* and *trans*): 22.1, 22.7, 26.8, 40.9, 41.9, 42.4, 68.8, 69.1, 203.8, 204.1. ^1H NMR (400 MHz, DMSO-d_6 -D_2O exchange, mixture of *cis* and *trans*): δ 0.94 (s, 3H), 0.96 (s, 3H), 1.85-2.22 (m, 5H), 2.86-2.90 (m, 1H), 9.53 & 9.71 (2 s, 1H).

Intermediate #2

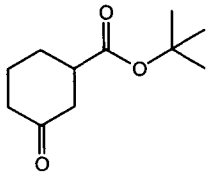


1-{[*tert*-Butyl(dimethyl)silyl]oxy}propan-2-ol

To a solution of propylene glycol (1.0 g, 13 mmol) in DCM (60.0 mL) was added *tert*-butyldimethylchlorosilane (2.0 g, 13 mmol) followed by DIPEA (3.2 mL, 18 mmol). The reaction mixture was stirred at ambient temperature for 18 hours. The solution was diluted with ether, washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford the title compound.

LRMS (ESI) calc'd for $C_9H_{22}O_2Si$ $[M+H]^+$: 191, Found: 191.

Intermediate #3

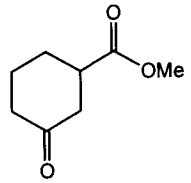


***tert*-Butyl 3-oxocyclohexanecarboxylate**

Anhydrous $MgSO_4$ (3.4 g, 28 mmol) was suspended in DCM (28.1 mL) and to this vigorously stirred mixture was added concentrated sulfuric acid (0.7 g, 7 mmol). The resulting mixture was allowed to stir at ambient temperature for 30 minutes. 3-Oxocyclohexanecarboxylic acid (1.0 g, 7.0 mmol) was added followed by *t*-BuOH (2.6 g, 35 mmol). The resulting mixture was allowed to stir for 24 hours before it was filtered and flushed with DCM. The filtrate was washed with water, and the organic layer was again washed with water, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford the title compound. The residue was used without further purification.

^1H NMR (500 MHz, $CDCl_3$): δ 2.72-2.64 (m, 1H), 2.47 (d, J = 8.1 Hz, 2H), 2.36-2.24 (m, 2H), 2.08-1.98 (m, 2H), 1.84-1.66 (m, 2H), 1.44 (s, 9H).

Intermediate #4

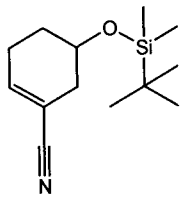


Methyl 3-oxocyclohexanecarboxylate

To a solution of 3-oxocyclohexanecarboxylic acid (1.0 g, 7.0 mmol) in diethyl ether (28 mL) was added dropwise TMS-diazomethane (3.5 mL, 7.0 mmol, 2.0 mL in diethyl ether). MeOH (30 mL) was added and the mixture was maintained at ambient temperature for 30 minutes. The mixture was concentrated *in vacuo*, and the residue was purified by MPLC on silica gel (using a gradient elution of 0-45% EtOAc/hexanes). Desired fractions were identified, combined, and concentrated *in vacuo* to afford the title compound.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.66 (s, 3H), 2.82-2.72 (m, 1H), 2.54-2.46 (m, 2H), 2.38-2.24 (m, 2H), 2.12-1.98 (m, 2H), 1.86-1.75 (m, 1H), 1.75-1.64 (m, 1H).

Intermediate #5

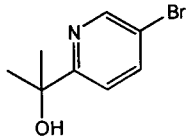


5-{[*tert*-Butyl(dimethyl)silyl]oxy}cyclohex-1-ene-1carbonitrile

5-Hydroxycyclohex-1-ene-1-carbonitrile (500 mg, 4.06 mmol) was dissolved in anhydrous DMF (5.1 mL) and then cooled to 0 °C. Imidazole (276 mg, 4.06 mmol) and TBS-Cl (612 mg, 4.06 mmol) were added and the reaction mixture was allowed to stir at 0 °C for 2 hours. The reaction mixture was partitioned between water and DCM. The organic layer was collected and the aqueous layer was again extracted with DCM. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 0-100%, EtOAc/hexanes) to afford the title compound. LRMS (ESI) calc'd for $C_{13}H_{23}NOSi$ $[M+H]^+$: 238, Found: 238.

Scheme #1

Intermediate #6



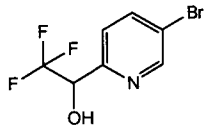
2-(5-Bromopyridin-2-yl)propan-2-ol

Methyl 5-bromopicolinate (500 mg, 2.31 mmol) was dissolved in THF (7.0 mL) and the flask was sealed with a septum and flushed with argon. The mixture was cooled to 0 °C and methylmagnesium bromide (3.1 mL, 9.3 mmol, 3M in THF) was added. The resulting mixture was allowed to stir at 0 °C for 1 hour before the reaction was quenched with saturated

aqueous ammonium chloride and extracted with EtOAc. The organic layer was then washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford the title compound, which was used without further purification. LRMS (ESI) calc'd for $C_8H_{10}BrNO$ $[M+H]^+$: 216, Found: 216.

Scheme #2

Intermediate #7

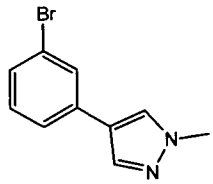


1-(5-Bromopyridin-2-yl)-2,2,2-trifluoroethanol

5-Bromopicolinaldehyde (500 mg, 2.70 mmol) was dissolved in THF (9.0 mL) and the flask was then sealed with a septum, flushed with argon, and cooled to 0 °C. (Trifluoromethyl)trimethylsilane (0.44 mL, 3.0 mmol) was then added followed by TBAF (2.7 mL, 2.7 mmol, 1M in THF). The resulting mixture was allowed to warm to ambient temperature and was stirred for 2 hours. The reaction was then quenched with water and extracted with DCM (2x). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 10-20% EtOAc/hexanes) to afford the title compound. LRMS (ESI) calc'd for $C_8H_6BrF_3O$ $[M+H]^+$: 256, Found: 256.

Scheme #3

Intermediate #8-1



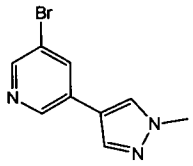
4-(3-Bromophenyl)-1-methyl-1*H*-pyrazole

1,3-Dibromobenzene (0.38 mL, 3.2 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (595 mg, 2.86 mmol), $Pd(dppf)Cl_2$ (260 mg, 0.320 mmol), and potassium phosphate (2.0 g, 9.5 mmol) were combined in a flask and dissolved in dioxane (16.0 mL) and water (1.6 mL). The flask was then sealed and flushed with argon. The reaction mixture was allowed to stir at 90 °C for 90 minutes. The mixture was then cooled to ambient temperature and diluted with EtOAc. The organic layer was washed with water, brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (50% EtOAc/hexanes) to afford the title compound.

LRMS (ESI) calc'd for $C_{10}H_9BrN_2$ $[M+H]^+$: 237, Found: 237.

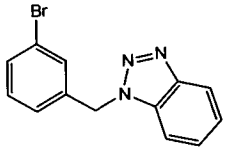
The following intermediates found in **TABLE 1** were prepared according to **Scheme #3** following similar procedures described for **Intermediate #8-1**, which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 1:

Intermediate	Structure	COMPOUND Name	Exact Mass $[M+H]^+$
8-2		3-bromo-5-(1-methyl-1*H*-pyrazol-4-yl)pyridine	Calc'd 238, Found 238

Scheme #4

Intermediate #9-1

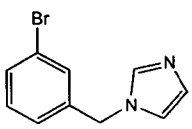


1-(3-Bromobenzyl)-1*H*-benzotriazole

To a solution of 1*H*-benzotriazole (0.52 g, 4.4 mmol) in THF (25 mL) was added potassium *tert*-butoxide (4.6 mL, 4.6 mmol, 1M in THF) followed by the addition of 1-bromo-3-(bromomethyl)benzene (1.0 g, 4.0 mmol). The solution was allowed to stir for 4 hours before the reaction was quenched with saturated aqueous $NaHCO_3$ and diluted with EtOAc. The organic layer was separated and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 0-80% EtOAc/hexanes) to afford the title compound as a white solid. LRMS (ESI) calc'd for $C_{13}H_{11}BrN_3$ $[M+H]^+$: 288, Found 288.

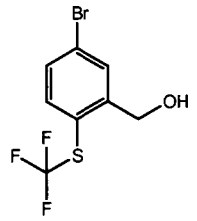
The following intermediates disclosed in **TABLE 2** were prepared according to **Scheme #4** following similar procedures described for **Intermediate #9-1**, which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 2:

Intermediate	Structure	Compound Name	Exact Mass $[M+H]^+$
9-2		1-(3-bromobenzyl)-1*H*-imidazole	Calc'd 237, Found 237

Scheme #6

Intermediate #10

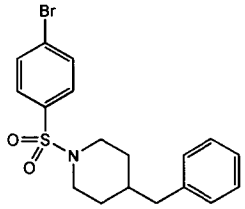


{5-Bromo-2-[(trifluoromethyl)sulfanyl]phenyl}methanol

NaH (120 mg, 3.01 mmol, 60% dispersion in oil) and 5-(trifluoromethyl)dibenzo[*b*,*d*]thiophenium trifluoromethanesulfonate (808 mg, 2.01 mmol) were added sequentially to a solution of (5-bromo-2-sulfanylphenyl)methanol (440 mg, 2.01 mmol) in DMF (10 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 45 minutes, and was then partitioned between EtOAc and water. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 0-20%, EtOAc/hexanes) to afford the title compound. ^1H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, J = 1.8 Hz, 1H), 7.53-7.48 (m, 2H), 4.92 (s, 2H), 2.02 (s, 1H).

Scheme #12

Intermediate #11

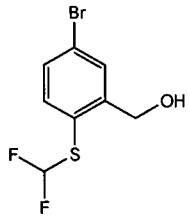


4-Benzyl-1-[(4-bromophenyl)sulfonyl]piperdine

4-Bromobenzene-1-sulfonyl chloride (100 mg, 0.391 mmol) dissolved in DCM (2.0 mL) at ambient temperature. 4-Benzylpiperdine (89 mg, 0.51 mmol) were diluted in DCM (2.0 mL) and treated with DIPEA (0.205 mL, 1.174 mmol) at ambient temperature. To this mixture a solution of 4-bromobenzene-1-sulfonyl chloride (100 mg, 0.391 mmol) dissolved in DCM (2.0 mL) was added and the reaction stirred at ambient temperature for 17 hours. The reaction was then concentrated *in vacuo* to afford the title compound, which was used without further purification. LRMS(ESI) calc'd for $C_{18}H_{20}BrNO_2S$ $[M+H\}^+$: 394; found 394

Scheme #13

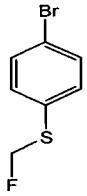
Intermediate #12



{5-Bromo-2-[(difluoromethyl)sulfanyl]phenyl}methanol

(5-Bromo-2-sulfanylphenyl)methanol (0.50 g, 2.8 mmol) was dissolved in MeCN (11.4 mL) followed by the addition of water (11.4 mL) and solid potassium hydroxide (2.56 g, 45.6 mmol). The mixture was plunged into a -78 °C bath and when the mixture began to freeze diethyl [bromo(difluoro)methyl]phosphonate (1.22 g, 4.56 mmol) was added all at once and the cold bath was removed. The mixture was allowed to warm to ambient temperature and was stirred for 20 minutes. The mixture was then partitioned between EtOAc and water. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 0-25% EtOAc/hexanes). Desired fractions were identified, combined, and concentrated *in vacuo* to afford the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.47 (m, 2H), 6.80 (t, J = 56.5 Hz, 1H), 4.87 (s, 2H), 1.96 (br s, 1H).

Intermediate #13

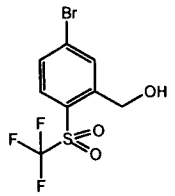


1-Bromo-4-[(fluoromethyl)sulfanyl]benzene

1-Bromo-4-(methylsulfinyl)benzene (1.50 g, 6.85 mmol) was dissolved in 1,2-DCE (14 mL) and stirred at ambient temperature. BAST (3.79 g, 17.1 mmol) was added dropwise followed by zinc iodide (0.07 g, 0.21 mmol). The reaction vessel was sealed and the mixture was heated to 40 °C, allowed to stir for 24 hours, and then allowed to cool to ambient temperature. The mixture was partitioned between EtOAc and water, the layers were separated and the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 0-20% EtOAc/hexanes). Desired fractions were identified, combined, and concentrated *in vacuo* to afford the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49-7.44 (m, 2H), 7.38-7.33 (m, 2H), 5.69 (d, J = 52.8 Hz, 2H).

Scheme #6

Intermediate #14-1



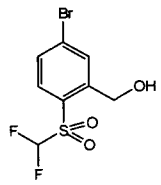
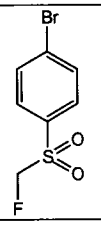
{5-Bromo-2-[(trifluoromethyl)sulfonyl]phenyl}methanol

A mixture of *m*-CPBA (452 mg, 2.62 mmol) and {5-bromo-2-[(trifluoromethyl)thio]phenyl}methanol (188 mg, 0.655 mmol) in DCM (6.6 mL) was heated to

40 °C and stirred in a microwave reaction vial for 30 hours. After cooling to 23 °C, the reaction mixture was partitioned between EtOAc and aqueous potassium bisulfate solution (40% w/w). The organic layer was washed sequentially with saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 0-30%, EtOAc/hexanes) to afford the title compound. ^1H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 1.7 Hz, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.73 (dd, J = 8.6, 2.0 Hz, 1H), 5.01 (s, 2H), 2.56 (s, 1H).

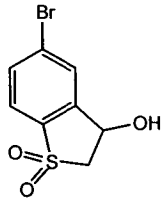
TABLE 3 discloses intermediates **14-2** and **14-3** that were prepared according to **Schemes #6-8** following similar procedures described for **Intermediate #14-1**, which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 3:

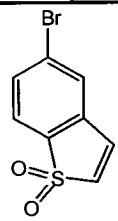
Intermediate	Structure	Compound Name	^1H NMR δ (ppm)
14-2		{5-bromo-2-[(difluoromethyl)sulfonyl]phenyl}methanol	^1H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, J = 1.9 Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.72 (dd, J = 8.3, 1.9 Hz, 1H), 6.33 (t, J = 53.6 Hz, 1H), 4.98 (d, J = 6.4 Hz, 2H), 2.53 (t, J = 6.4 Hz, 1H).
14-3		1-bromo-4-[(fluoromethyl)sulfonyl]benzene	^1H NMR (500 MHz, $CDCl_3$): δ 7.86-7.80 (m, 2H), 7.80-7.74 (m, 2H), 5.13 (d, J = 46.9 Hz, 2H).

Scheme #15

Intermediate #15



5-Bromo-2,3-dihydro-1-benzothiophene-3-ol 1,1-dioxide



Step A: **5-Bromo-1-benzothiophene 1,1-dioxide**

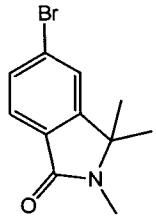
5-Bromo-1-benzothiophene (1.50 g, 7.04 mmol) was dissolved in chloroform (47 mL) and allowed to stir vigorously at ambient temperature. *m*-CPBA (4.34 g, 17.6 mmol) was added in three portions and the resulting mixture was maintained at ambient temperature for 16 hours. The mixture was then diluted with 1M aqueous sodium thiosulfate and extracted with EtOAc. The organic layer was again washed with 1M aqueous sodium thiosulfate, saturated aqueous $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 0-30% EtOAc/hexanes). Desired fractions were identified, combined, and concentrated *in vacuo* to afford the title compound. ^1H NMR (600 MHz, $CDCl_3$): δ 7.65 (dd, J= 7.9, 1.8 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.50 (d, J = 1.8 Hz, 1H), 7.15 (d, J = 6.9 Hz, 1H), 6.74 (d, J = 6.9 Hz, 1H).

Step B: **5-Bromo-2,3-dihydro-1-benzothiophene-3-ol 1,1-dioxide**

5-Bromo-1-benzothiophene 1,1-dioxide (100 mg, 0.41 mmol) was suspended in 1N aqueous sodium hydroxide (2.0 mL), heated to 100 °C in a microwave, and allowed to stir for 15 minutes. The mixture was then allowed to cool to ambient temperature before the mixture was diluted with saturated aqueous ammonium chloride and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was used without further purification. LRMS (ESI) calc'd for $C_8H_7BrO_3S$ $[M+Na]^+$: 285, Found: 285.

Scheme #16

Intermediate #16



5-Bromo-2,3,3-trimethyl-2,3-dihydro-1*H*-isoindol-1-one

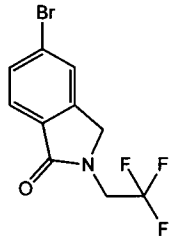
5-Bromo-2,3-dihydro-1*H*-isoindol-1-one (150 mg, 0.71 mmol) was dissolved in DMF (3.5 mL) and stirred at ambient temperature. NaH (85 mg, 2.1 mmol, 60% dispersion in oil) was carefully added in two portions, and the resulting mixture was allowed to stir for 15 minutes before MeI (151 mg, 1.06 mmol) was added. The mixture was allowed to stir at ambient temperature for 30 minutes before water (10 mL) was carefully added. The mixture was

extracted with EtOAc, and the organic layer was washed with water, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 0-20% EtOAc/hexanes). Desired fractions were identified, combined, and concentrated *in vacuo* to afford the title compound.

LRMS (ESI) calc'd for $C_{11}H_{12}BrNO$ $[M+H]^+$: 254, Found: 254.

Scheme #17

Intermediate #17



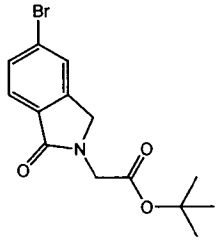
5-Bromo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-isoindol-1-one

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% 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 by MPLC on silica gel (using a gradient elution of 0-20% EtOAc/hexanes). Desired fractions were identified, combined, and concentrated *in vacuo* to afford the title compound.

LRMS (ESI) calc'd for $C_{10}H_7BrF_3NO$ $[M+H]^+$: 294, Found: 294.

Scheme #17

Intermediate #18



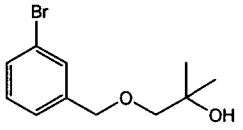
***tert*-Butyl (5-bromo-1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)acetate**

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% dispersion in oil) was carefully added in two portions, and the resulting mixture was allowed to stir at 0 °C for 15 minutes before *tert*-butyl bromoacetate (92 mg, 0.47 mmol) was added. The mixture was allowed to stir at 0 °C

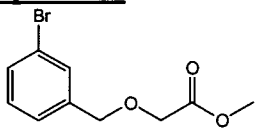
for 30 minutes before saturated aqueous $NaHCO_3$ (10 mL) was carefully added. The mixture was extracted with EtOAc, and the organic layer was washed with water, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 0-20% EtOAc/hexanes). Desired fractions were identified, combined, and concentrated *in vacuo* to afford the title compound. LRMS (ESI) calc'd for $C_{14}H_{16}BrNO_3$ $[M+Na]^+$: 348, Found: 348.

Scheme #5

Intermediate #19



1-[(3-Bromobenzyl)oxy]-2-methylpropan-2-ol



Step A: **Methyl [(3-bromobenzyl)oxy]acetate**

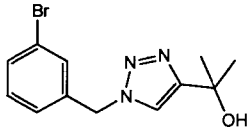
Methyl hydroxyacetate (0.80 g, 8.8 mmol) was dissolved in THF (10 mL) and allowed to stir at 0 °C under a nitrogen atmosphere. NaH (0.40 g, 9.6 mmol, 60% dispersion in oil) was added portionwise over approximately 5 minutes. The cooling bath was removed and the reaction mixture was allowed to warm to ambient temperature. 1-Bromo-3-(bromomethyl)benzene (2.0 g, 8.0 mmol) was added in a single portion and the resulting mixture was heated to 40 °C. After 4 hours, the reaction mixture was allowed to cool to ambient temperature and partitioned between water and EtOAc. The layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title compound, which was carried forward without further purification. ^1H NMR (600 MHz, $CDCl_3$): δ 7.53-7.50 (m, 1H), 7.42-7.38 (m, 1H), 7.30-7.17 (m, 2H), 4.57 (s, 2H), 4.09 (s, 2H), 3.74 (s, 3H).

Step B: **1-[(3-Bromobenzyl)oxy]-2-methylpropan-2-ol**

Methyl [(3-bromobenzyl)oxy]acetate (2.0 g, 7.7 mmol) was dissolved in THF (10 mL) and was allowed to stir under a nitrogen atmosphere. Methylmagnesium bromide (7.7 mL, 23 mmol, 3.0 M in THF) was added dropwise. The reaction mixture was allowed to stir at ambient temperature for 4 hours before the reaction was quenched with water and the mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 2-70% EtOAc/hexanes). Desired fractions were identified, combined, and concentrated *in vacuo* to the title compound. ^1H NMR (600 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.25-7.18 (m, 2H), 4.52 (s, 2H), 3.29 (s, 2H), 1.21 (s, 6H).

Scheme #4

Intermediate #20

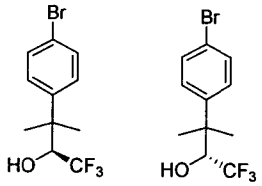


Step A-B: **2-[1-(3-Bromobenzyl)-1*H*-1,2,3-triazol-4-yl]propan-2-ol**

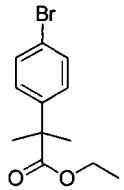
To a solution of 1-bromo-3-(bromomethyl)benzene (5.0 g, 20 mmol) in DMSO (40 mL) was added sodium azide (1.3 g, 20 mmol). The resulting mixture was allowed to stir at ambient temperature for 18 hours before it was diluted with water and extracted with diethyl ether (2x). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was dissolved in ^tBuOH (65 mL and water (39 mL) and to this mixture was added 2-methylbut-3-yn-2-ol (2.3 g, 27 mmol), and then a solution of copper (II) sulfate pentahydrate (0.26 g, 1.0 mmol) in water (10 mL) followed by a solution of sodium ascorbate (0.83 g, 4.2 mmol) in water (8 mL). The resulting mixture was allowed to stir at ambient temperature for 2 hours before it was diluted with water and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was used without further purification. LRMS (ESI) calc'd for $C_{12}H_{14}BrN_3O$ $[M+H]^+$: 296, Found: 296.

Scheme #7

Intermediate#21-1 and 21-2



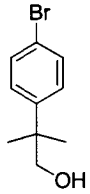
(*S* or *R*)-3-(4-Bromophenyl)-1,1,1-trifluoro-3-methylbutan-2-ol



Step A: **Ethyl 2-(4-bromophenyl)-2-methylpropanoate**

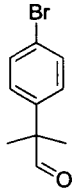
To a stirred solution of ethyl 2-(4-bromophenyl)acetate (10 g, 41 mmol) in THF(80 mL) under nitrogen was added sodium hydride (4.9 g, 60 %, 123 mmol) in portions at 0 °C. The resulting solution was stirred at 0 °C for 30 minutes before the addition of iodomethane (17 g, 123 mmol) at 0 °C. The resulting mixture was stirred at ambient temperature for additional 1 hour before the reaction was quenched with saturated NH_4Cl aqueous solution (20 mL) at 0 °C. The solution was extracted with EtOAc(3x100 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by MPLC

on silica gel (eluting with 1-2 % EtOAc/hexane) to afford the title compound as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 6.8 Hz, 2H), 7.24 (d, J = 6.8 Hz, 2H), 4.14 (q, J = 7.2 Hz, 2H), 1.58 (s, 6H), 1.20 (t, J = 7.2 Hz, 3H). MS ESI: $[M+H]^+$ *m/z* 271, 273.



Step B: **2-(4-Bromophenyl)-2-methylpropan-1-ol**

To a solution of 2-(4-bromophenyl)-2-methylpropanoate (8.9 g, 33 mmol) in THF(100 mL) under nitrogen was added $LiAlH_4$ (1.6 g, 43 mmol) in portions at 0 °C. The resulting solution was stirred at 0 °C for 1 hour before the addition of saturated aqueous NH_4Cl (50 mL). The mixture was then extracted with EtOAc (3x80 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by MPLC on Silica gel with 2-5 % EtOAc/hexane to afford 2-(4-bromophenyl)-2-methylpropan-1-ol as a colorless oil. MS ESI: $[M+H]^+$ *m/z* 229, 231; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 6.8 Hz, 2H), 7.28 (d, J = 6.8 Hz, 2H), 3.61 (s, 2H), 1.58 (s, 6H).



Step C: **2-(4-Bromophenyl)-2-methylpropanal**

To a stirred solution of 2-(4-bromophenyl)-2-methylpropan-1-ol (10 g, 44 mmol) in dichloromethane (80 mL) was added PCC (14 g, 65 mmol) in portions at 0 °C. The resulting solution was stirred at ambient temperature for 16 hours, and then filtered and concentrated *in vacuo*. The crude residue was purified by MPLC on silica gel (eluting with 1-2 % EtOAc /hexane) to afford the title compound as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.52 (d, J = 6.3 Hz, 2H), 7.17 (d, J = 6.3 Hz, 2H), 1.43 (s, 6H).

Step D: **(S or R)-3-(4-Bromophenyl)-1,1,1-trifluoro-3-methylbutan-2-ol**

To a solution of 2-(4-bromophenyl)-2-methylpropanal (5.7 g, 25 mmol) and trimethyl(trifluoromethyl)silane (7.1 g, 50 mmol) in THF(60 mL) under nitrogen was added a solution of TBAF (0.66 g, 2.5 mmol) in THF(10 mL) dropwise at -30 °C. The resulting solution was stirred at -30 °C for 1 hour and at ambient temperature for an additional 1 hour before the addition of 1 N aqueous HCl (20 mL). The mixture was vigorously stirred at ambient temperature for 10 minutes, and then extracted with EtOAc(3x100 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by MPLC on Silica gel (eluting with 2-4 % EtOAc/hexane) to afford (*S* and *R*)-3-(4-

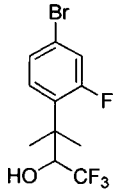
bromophenyl)-1,1,1-trifluoro-3-methylbutan-2-ol as a light yellow oil. The racemic mixture was resolved by preparative chiral HPLC (Chiralpak IA, 2*25cm; Mobile phase: 5 % ethanol in hexane) to afford the two enantiopure title compounds.

Intermediate #21-1: 1st peak to elute: (*S* or *R*)-3-(4-bromophenyl)-1,1,1-trifluoro-3-methylbutan-2-ol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.28 – 7.23 (m, 2H), 4.10 – 3.97 (m, 1H), 2.08 (br, 1H), 1.44 (s, 6H). MS GC: $[M]^+$ *m/z* 295, 297.

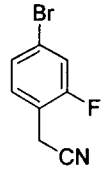
Intermediate #21-2: 2nd peak to elute: (S or *R*)-3-(4-bromophenyl)-1,1,1-trifluoro-3-methylbutan-2-ol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.28 – 7.23 (m, 2H), 4.10 – 3.97 (m, 1H), 2.08 (br, 1H), 1.44 (s, 6H). MS GC: $[M]^+$ *m/z* 295, 297.

Scheme #8

Intermediate #22

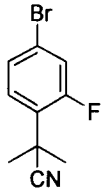


(S and R)-3-(4-Bromo-2-fluorophenyl)-1,1,1-trifluoro-3-methylbutan-2-ol



Step A: **2-(4-Bromo-2-fluorophenyl)acetonitrile**

A solution of 4-bromo-1-(bromomethyl)-2-fluorobenzene (20 g, 74 mmol) and potassium cyanide (10 g, 150 mmol) in ethanol (150 mL) and water (30 mL) was stirred at 70 °C for 1 hour. The resulting solution was diluted with water (50 mL), and then extracted with EtOAc (3x200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by MPLC on Silica gel (eluting with 2-5 % EtOAc/hexane) to afford the title compound as a light yellow oil. ^{1}H NMR (400 MHz, CDCl3) δ 7.38 – 7.22 (m, 3H), 3.74 (s, 2H). MS ESI: [M+H]+ *m/z* 214.

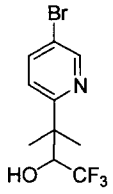


Step B: **2-(4-bromo-2-fluorophenyl)-2-methylpropanenitrile**

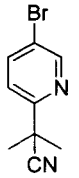
To the solution of 2-(4-bromo-2-fluorophenyl)acetonitrile (6.0 g, 28 mmol) in THF(80 mL) was added sodium hydride (3.4 g, 60 %, 140 mmol) in portions at 0 °C. The resulting solution was stirred at 0 °C for 30 minutes before the addition of iodomethane (12 g, 83 mmol) at 0 °C. The mixture was stirred at ambient temperature for additional 1 hour before the

Scheme #9

Intermediate #23

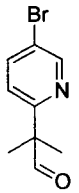


(*S* and *R*)-3-(5-Bromopyridin-2-yl)-1,1,1-trifluoro-3-methylbutan-2-ol



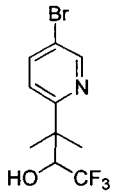
Step A: **2-(5-Bromopyridin-2-yl)-2-methylpropanenitrile**

To a solution of 2,5-dibromopyridine (5.0 g, 21 mmol) and 2-methylpropanenitrile (1.6 g, 23 mmol) in toluene (50 mL) under nitrogen was added NaHMDS (12 mL, 23 mmol, 2.0M in THF) dropwise at 0 °C. The resulting solution was stirred at ambient temperature overnight before the addition of saturated aqueous NH_4Cl (20 mL). The resulting mixture was extracted with EtOAc (3x30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by MPLC on Silica gel (eluting with 1-3 % EtOAc/hexane) to afford the title compound as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.85 (d, J = 8.7 Hz, 1H), 7.51 (d, J = 8.7 Hz, 1H), 1.75 (s, 6H). MS ESI $[M+H]^+$ *m/z* 225, 227.



Step B: **2-(5-Bromopyridin-2-yl)-2-methylpropanal**

To a solution of 2-(5-bromopyridin-2-yl)-2-methylpropanenitrile (2.0 g, 8.9 mmol) in dichloromethane (20 mL) under nitrogen was added DIBAL-H (12.4 mL, 12.4 mmol, 1.0 M in THF) dropwise at -30 °C. The resulting solution was stirred at ambient temperature for 3 hours before the addition of 2 N aqueous HCl (10 mL) at 0 °C. The resulting solution was stirred at ambient temperature for 10 minutes, the solution was basified with saturated aqueous $NaHCO_3$ to pH 8-9, and then extracted with EtOAc (3x20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by MPLC on Silica gel (eluting with 2-4 % EtOAc/hexane) to afford the title compound as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.66 (s, 1H), 7.82 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 8.7 Hz, 1H), 1.47 (s, 6H). MS ESI: $[M+H]^+$ *m/z* 228, 230.

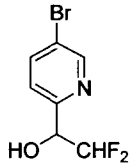


Step C: **(*S* and *R*)3-(5-Bromopyridin-2-yl)-1,1,1-trifluoro-3-methylbutan-2-ol**

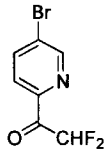
To a solution of 2-(5-bromopyridin-2-yl)-2-methylpropanal (1.0 g, 4.4 mmol) and trimethyl(trifluoromethyl)silane (1.1 g, 7.5 mmol) in THF (10 mL) under nitrogen was added the solution of TBAF (230 mg, 0.88 mmol) in THF (5 mL) dropwise at -30 °C. The resulting solution was stirred at -30 °C for 1 hour and at ambient temperature for additional 1 hour before the addition of the second batch of TBAF (1.1 g, 4.4 mmol) at ambient temperature. The resulting mixture was stirred at ambient temperature for 20 minutes, then the reaction solution was diluted with water (10 mL), and extracted with EtOAc (3x15 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by MPLC on Silica gel (eluting with 2-5 % EtOAc/hexane) to afford the title compound as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.86 (d, J = 8.7 Hz, 1H), 7.24 (d, J = 8.7 Hz, 1H), 4.01 (q, J = 7.8 Hz, 1H), 1.51 (s, 6H). MS ESI: $[M+H]^+$ *m/z* 298, 300.

Scheme #10

Intermediate #24



(*S* and *R*)-1-(5-Bromopyridin-2-yl)-2,2-difluoroethanol



Step A: **1-(5-Bromopyridin-2-yl)-2,2-difluoroethanone**

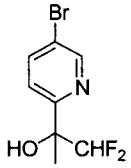
To the solution of 2,5-dibromopyridine (16 g, 67 mmol) in toluene (150 mL) was added *n*-BuLi (27 mL, 67 mmol) dropwise at -78 °C. The resulting solution was stirred at -78 °C for 1 hour before the addition of 2,2-difluoroacetate (10 g, 80 mmol). The mixture was stirred at ambient temperature for 16 hours, then diluted with saturated aqueous NH_4Cl (80 mL) at 0 °C, and extracted with EtOAc (2x100 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by MPLC on Silica gel (eluting with 5-10 % EtOAc/hexane) to afford the title compound as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.08 (d, J = 6.0 Hz, 1H), 8.03 (d, J = 6.0 Hz, 1H), 7.05 (t, J = 54.4 Hz, 1H).

Step B: **1-(5-Bromopyridin-2-yl)-2,2-difluoroethanol**

To a solution of 1-(5-bromopyridin-2-yl)-2,2-difluoroethanone (1.0 g, 4.2 mmol) in methanol (10 mL) was added $NaBH_4$ (180 mg, 4.6 mmol) at 0 °C. The resulting solution was stirred at ambient temperature for 2 hours before the addition of saturated aqueous NH_4Cl (5 mL) at 0 °C. Methanol was removed *in vacuo*, and the resulting aqueous solution was extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford the title compound as an off-white solid, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.91 (d, J = 6.0 Hz, 1H), 7.52 (d, J = 6.0 Hz, 1H), 5.89 (td, J = 54.4, 3.9 Hz, 1H), 4.92 – 4.84 (m, 1H), 4.52 (br, 1H).

Scheme #10

Intermediate 25

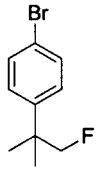


(*S* and *R*)-2-(5-Bromopyridin-2-yl)-1,1-difluoropropan-2-ol

To a solution of 1-(5-bromopyridin-2-yl)-2,2-difluoroethanone (1.5 g, 6.4 mmol) in THF (15 mL) under nitrogen was added MeMgBr (3.2 mL, 9.6 mmol, 3.0 M in THF) dropwise at -15 °C. The resulting solution was stirred at ambient temperature for 2 hours before the addition of saturated aqueous NH_4Cl (10 mL) at 0 °C. The resulting mixture was vigorously stirred for 10 minutes, and then extracted with EtOAc (3x20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by MPLC on Silica gel (eluting with 1-3 % EtOAc/hexane) to afford the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, J = 2.0 Hz, 1H), 7.92 (dd, J = 8.4, 2.0 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 5.76 (t, J = 56.4 Hz, 1H), 5.22 (br, 1H), 1.60 (s, 3H).

Scheme #11

Intermediate #26



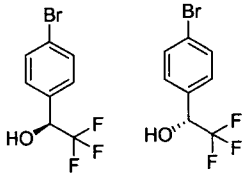
1-Bromo-4-(1-fluoro-2-methylpropan-2-yl)benzene

2-(4-bromophenyl)-2-methylpropan-1-ol (500 mg, 2.182 mmol) was dissolved in Dichloromethane (7.2 mL) in a 20 mL vial. DAST (0.433 mL, 3.27 mmol) was then slowly added to the solution. Stirred at ambient temperature overnight. TLC showed presence of starting material. Another 0.5 eq. of DAST was added and stirred for 4 hours. TLC then showed

consumption of starting material. The reaction was loaded directly on a silica column and the column was then dried out. Purified with a Teledyne Isco Combiflash Rf purification system using a gradient of 5% EtOAc/hexanes. Isolated 1-bromo-4-(1-fluoro-2-methylpropan-2-yl)benzene as a clear liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.42 (d, 2H), 7.10 – 7.09 (d, 2H), 2.88 (s, 1H), 2.83 (s, 1H), 1.35 (s, 3H), 1.30 (s, 3H).

Scheme #10

Intermediate #27-1 and #27-2



1(*S* or *R*)-(4-Bromophenyl)-2,2,2-trifluoroethanol

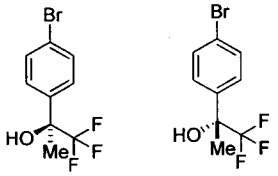
4'-Bromo-2,2,2-trifluoroacetophenone (3.00 mL, 19.8 mmol) was stirred in MeOH (66 mL) at 0 °C. Sodium borohydride (0.748 g, 19.8 mmol) was added and the mixture was allowed to warm to ambient temperature. The mixture was stirred for 3 hours, then quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was then washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by MPLC (eluting with 5% EtOAc/hexanes). Desired fractions were identified, combined, and concentrated *in vacuo* to afford a racemic mixture of the title compounds. The racemic residue was resolved by Chiral SFC purification (Chiral Technology OJ-H 2.1 X 25cm, 5uM Column; eluting with 5% isopropyl alcohol/CO2).

Intermediate 27-1: 1st peak to elute; (S or R)-1-(4-bromophenyl)-2,2,2-trifluoroethanol ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.54 (d, 2H), 7.37 – 7.35 (d, 2H), 5.03 – 4.98 (m, 1H), 2.79 (bs, 1H).

Intermediate 27-2: 1st peak to elute; (S or R)-1-(4-bromophenyl)-2,2,2-trifluoroethanol. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.54 (d, 2H), 7.37 – 7.35 (d, 2H), 5.03 – 4.98 (m, 1H), 2.79 (bs, 1H).

Scheme #10

Intermediate #28-1 and #28-2



(*S* or *R*)-2-(4-Bromophenyl)-1,1,1-trifluoropropan-2-ol

4'-Bromo-2,2,2- trifluoroacetophenone (1.80 mL, 11.9 mmol) was stirred in THF (60 mL) at 0 °C under an argon atmosphere. Methylmagnesium bromide (19.8 mL, 59.3 mmol) was added and the reaction mixture was stirred at 0 °C for 1 hour and then allowed to warm to ambient temperature overnight. The reaction was quenched with saturated aqueous ammonium

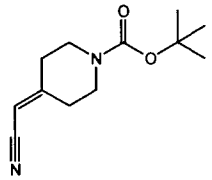
chloride and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 0-25% EtOAc/hexanes). Desired fractions were identified, combined, and concentrated *in vacuo* to afford a racemic mixture of the title compounds. The racemic residue was resolved by Chiral SFC purification (Chiral Technology AZ-H 2.1 X 25cm, 5uM column, eluted with 5% methanol).

Intermediate 28-1: 1st peak to elute; (*S* or *R*)-2-(4-Bromophenyl)-1,1,1-trifluoropropan-2-ol. ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.52 (d, 2H), 7.46 – 7.45 (d, 2H), 2.64 (bs, 1H), 1.76 (s, 3H).

Intermediate 28-2: 1st peak to elute; (*S* or *R*)-2-(4-Bromophenyl)-1,1,1-trifluoropropan-2-ol. ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.52 (d, 2H), 7.46 – 7.45 (d, 2H), 2.64 (bs, 1H), 1.76 (s, 3H).

Scheme #19

Intermediate #29-1



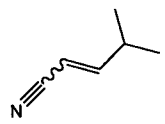
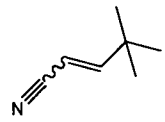
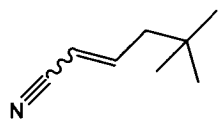
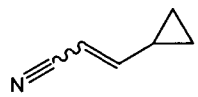
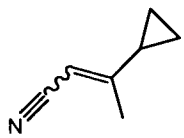
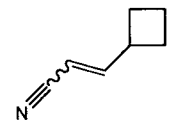
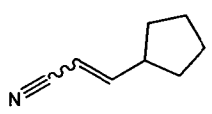
***tert*-Butyl 4-(cyanomethylidene)piperidine-1-carboxylate**

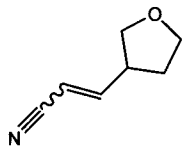
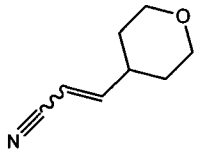
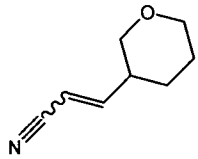
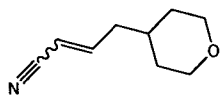
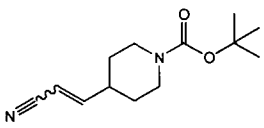
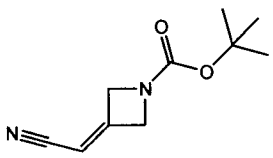
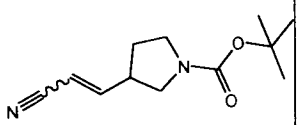
To a three necked round bottom flask equipped with a mechanical stirring bar was added potassium *tert*-butoxide (263 mL, 263 mmol, 1.0 M in THF) and THF (200 mL). The mixture was cooled to 0 °C, followed by the addition of diethyl (cyanomethyl)phosphonate (43.7 mL, 276 mmol) slowly by syringe. The reaction 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 (700 mL x2). 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.

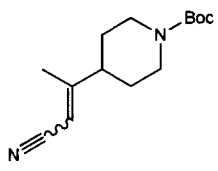
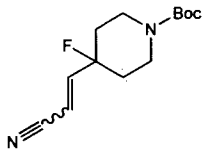
^1H-NMR (600 MHz, $CDCl_3$) δ 5.19 (s, 1H), 3.48-3.53 (m, 4H), 2.56 (t, J = 5.4Hz, 2H), 2.33 (t, J = 5.4Hz, 2H), 1.47 (s, 9H).

TABLE 4 discloses Intermediates 29-2 through 29-18 that were prepared according to **Scheme #19** following similar procedures described for **Intermediate #29-1**, which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 4:

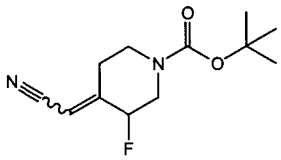
Interme -diate	Structure	Compound Name	Exact Mass $[M+H]^+$ or ^1H NMR δ (ppm)
29-2		(2E and Z)-4-methylpent-2-enenitrile	^1H NMR (600 MHz, $CDCl_3$): 1:1 E:Z δ 6.68 (dd, J = 16.4, 6.6, 1H), 5.27 – 5.23 (m, 1H), 1.96-1.82 (m, 1H), 1.04 (d, J = 6.8, 6H); ^1H NMR (600 MHz, $CDCl_3$): δ 6.31 – 6.24 (m, 1H), 5.18 (d, J = 10.9, 1H), 1.77 – 1.64 (m, 1H), 1.06 (d, J = 6.6, 6H).
29-3		(2E and Z)-4,4-dimethylpent-2-enenitrile	^1H NMR (600 MHz, $CDCl_3$): 1:1 E:Z δ 6.70 (d, J = 16.6, 1H), 5.20 (d, J = 12.3, 5.20, 1H), 1.22 (s, 9H); ^1H NMR (600 MHz, $CDCl_3$): δ 6.32 (d, J = 12.3, 1H), 5.22 (d, J = 16.6, 1H), 1.05 (s, 9H).
29-4		(2E and Z)-5,5-dimethylhex-2-enenitrile	^1H NMR (600 MHz, $CDCl_3$): 1:1 E:Z δ 6.72 (dt, J = 15.9, 7.9, 1H), 5.30 (dt, J = 15.2, 1.49, 1H), 2.08 (dd, J = 7.9, 1.3, 2H), 0.91 (s, 9H). ^1H NMR (600 MHz, $CDCl_3$) δ 6.53 (dt, J = 11.0, 8.0, 1H), 5.37 (dt, J = 11.0, 1.1, 1H), 2.30 (d, J = 8.0, 2H), 2, 0.95 (s, 9H).
29-5		(2E and 2Z)-3-cyclopropylprop-2-enenitrile	^1H NMR (600 MHz, $CDCl_3$): 5:3 E:Z δ 6.10-6.04 (m, 1H), 5.30 (d, J = 16.1 Hz, 1H), 1.58-1.50 (m, 1H), 1.04-0.92 (m, 4H); ^1H NMR (600 MHz, $CDCl_3$): δ 5.74 (t, J = 10.6, 1H), 5.12 (d, J = 10.6 Hz, 1H), 1.98-1.90 (m, 1H), 0.65 -0.58 (m, 4H).
29-6		(2E and Z)-3-cyclopropylbut-2-enenitrile	^1H NMR (600 MHz, $CDCl_3$): 3:1 E:Z δ 5.09-5.07 (m, 1H), 1.82-1.81 (m, 3H), 1.53 (t, J = 1.1, 1H), 0.87 – 0.81 (m, 2H), 0.70 – 0.65 (m, 2H); ^1H NMR (600 MHz, $CDCl_3$): δ 5.07-5.06 (m, 1H), 2.17 – 2.11 (m, 1H), 1.59-1.54 (m, 3H), 0.94 – 0.88 (m, 2H), 0.78 – 0.74 (m, 2H).
29-7		(2E and Z)-3-cyclobutylprop-2-enenitrile	^1H NMR (600 MHz, $CDCl_3$): 1:1 E:Z δ 6.78 (dd, J = 16.3, 6.8, 1H), 5.21 (dd, J = 16.3, 1.5, 1H), 2.30 – 1.85 (m, 7H); ^1H NMR (600 MHz, $CDCl_3$): δ 6.53 (dd, J = 10.8, 9.4, 1H), 5.12 (dd, J = 10.9, 0.8, 1H), 2.30 – 1.85 (m, 7H).
29-8		(2E and 2Z)-3-cyclopentylprop-2-enenitrile	^1H NMR (600 MHz, $CDCl_3$): 4:5 E:Z δ 6.68-6.64 (m, 1H), 5.26 (d, J = 17.6 Hz, 1H), 2.60-2.50 (m, 1H), 1.96-1.28 (m, 8H); ^1H NMR (600 MHz, $CDCl_3$): δ 6.34 (t, J = 10.6, 1H), 5.18 (d, J = 10.9 Hz, 1H), 3.04-2.94 (m, 1H), 1.96-1.28 (m, 8H).

29-9		(2E and 2Z)-3-(tetrahydrofuran-3-yl)prop-2-enenitrile	^{1}H NMR (600 MHz, $CDCl_3$): 1:1 E:Z δ 6.63 (dd, J = 16.3, 8.8, 1H), 6.39 (t, J = 10.5, 1H), 5.40 – 5.35 (m, 1H), 5.31 (d, J = 10.8, 1H), 3.97 – 3.87 (m, 4H), 3.82-3.77 (m, 2H), 3.56 – 3.50 (m, 2H), 3.46-3.39 (m, 1H), 3.02 – 2.92 (m, 1H), 2.27-2.27 (m, 1H), 2.19-2.13 (m, 1H), 1.79-1.67 (m, 2H).
29-10		(2E and 2Z)-3-(tetrahydro-2*H*-pyran-4-yl)prop-2-enenitrile	^{1}H NMR (600 MHz, $CDCl_3$): 1:1 E:Z δ 6.64 (dd, J = 16.5, 6.6, 1H), 5.29 (dd, J = 16.5, 1.6, 1H), 1.77 – 1.66 (m, 1H), 1.65 – 1.59 (m, 4H), 1.56 – 1.43 (m, 4H); ^{1}H NMR (600 MHz, $CDCl_3$): 6.28 (dd, J = 10.8, 9.8, 1H), 5.27 – 5.25 (m, 1H), 3.99 – 3.93 (m, 4H), 3.42 (dtd, J = 34.3, 11.8, 2.2, 4H), 2.43 – 2.33 (m, 1H).
29-11		(2E and 2Z)-3-(tetrahydro-2*H*-pyran-3-yl)prop-2-enenitrile	^{1}H NMR (600 MHz, $CDCl_3$): 3:5 E:Z δ 6.58 (dd, J = 16.5, 7.3, 1H), 5.36 (dd, J = 16.5, 1.4, 1H), 3.88-1.44 (m, 9H); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.37 (t, J = 10.5 1H), 5.33 (dd, J = 11.0, 0.6, 1H), 3.88-1.44 (m, 9H).
29-12		(2E and 2Z)-4-(tetrahydro-2*H*-pyran-4-yl)but-2-enenitrile	^{1}H NMR (600 MHz, $CDCl_3$): 1:1E:Z δ 6.66 (dt, J = 16.2, 7.6, 1H), 5.33 (dt, J = 16.3, 1.5, 1H), 3.97-3.89 (m, 8H), 2.18 – 2.14 (m, 2H), 1.78-1.54 (m, 1H); ^{1}H NMR (600 MHz, $CDCl_3$): 6.48 (dt, J = 10.9, 7.8, 1H), 5.37 (dt, J = 10.9, 1.2, 1H), 3.38 – 3.31 (m, 8H), 2.37 (t, J = 7.3, 2H), 1.78-1.54 (m, 1H).
29-13		*tert*-butyl 4-[(E and Z)-2-cyanoethenyl] piperidine-1-carboxylate	^{1}H NMR (500 MHz, $CDCl_3$): 18:5 E:Z δ 6.70-6.62 (m, 1H), 5.36-5.28 (m,1H), 4.25-4.05 (m, 2H), 2.85-2.65 (m, 2H), 2.35-2.25 (m, 1H), 1.75-1.68 (m, 2H), 1.46 (s, 9H), 1.38-1.20 (m, 2H); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.28 (t, J = 10.4, 1H), 5.29 (d, J = 10.9 Hz, 1H), 4.25-4.00 (m, 2H), 2.90-2.70 (m, 3H), 1.75-1.65 (m, 2H), 1.46 (s, 9H), 1.43-1.30 (m, 2H).
29-15		*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).
29-16		*tert*-butyl 3-[(E and Z)-2-cyanoethenyl] pyrrolidine-1-	^{1}H NMR (600 MHz, $CDCl_3$): 4:1 E:Z δ 6.37 (t, J = 10.6 Hz, 1H), 5.35 (d, J = 10.6 Hz, 1H), 3.70-2.86 (m, 5H), 2.20-2.00 (m, 1H), 1.84-1.70 (m, 1H), 1.43 (s, 9H); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.68-6.60 (m,

		carboxylate	1H), 5.35 (dd, J = 16.4, 1.2 Hz, 1H), 3.70-2.86 (m, 5H), 2.20-2.00 (m, 1H), 1.84-1.70 (m, 1H), 1.43 (s, 9H).
29-17		*tert*-butyl 4-[(1E and Z)-1-cyanoprop-1-en-2-yl]piperidine-1-carboxylate	Calc'd 251, Found 195 ($M+H-C_4H_8$)
29-18		*tert*-butyl 4-[(E and Z)-2-cyanoethenyl]-4-fluoropiperidine-1-carboxylate	Calc'd 255, Found 199 ($M+H-C_4H_8$)

Scheme #19

Intermediate #30

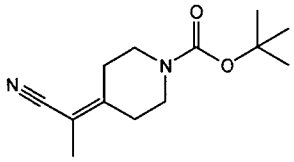


***tert*-Butyl (4E and 4Z)-4-(cyanomethylidene)-3-fluoropiperidine-1-carboxylate**

To a solution of NaH (0.27 g, 6.6 mmol, 60% in mineral oil) in DMF (10 mL) was added diethyl (cyanomethyl)phosphonate (1.5 g, 6.6 mmol). The mixture was stirred at ambient temperature for 30 minutes before *tert*-butyl 3-fluoro-4-oxopiperidine-1-carboxylate (0.70 g, 3.3 mmol) was added. The resulting mixture was stirred for 1 hour before the reaction was quenched with water and the mixture was concentrated *in vacuo*. The crude residue was purified by MPLC on silica gel to afford the title compound. LRMS (ESI) calc'd for ($C_{12}H_{18}FN_2O_2$) $[M+H]^+$: 241, Found 241.

Scheme #19

Intermediate #31

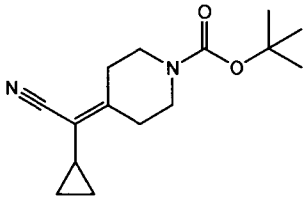


***tert*-Butyl 4-(1-cyanoethylidene)piperidine-1-carboxylate**

To a solution of MeI (1.42 g, 10 mmol) in DMF was added NaH (0.40 g, 10 mmol, 60% in mineral oil), followed by diethyl (cyanomethyl)phosphonate (2.35g, 10 mmol). The mixture was stirred at ambient temperature. After 30 minutes another batch of NaH (0.40 g, 10 mmol, 60% in mineral oil) was added, followed by *tert*-butyl 4-oxopiperidine-1-carboxylate (2.0 g, 10 mmol). The resulting mixture was stirred for 30 minutes before the reaction was quenched with water and the mixture was concentrated *in vacuo*. The crude residue was purified by MPLC on silica gel to afford the title compound. LRMS (ESI) calc'd for $C_{13}H_{21}N_2O_2$ $[M+H]^+$ 237, Found 237.

Scheme #19

Intermediate #32

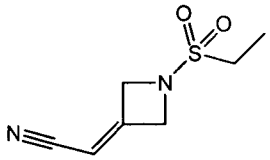


***tert*-Butyl 4-[cyano(cyclopropyl)methylidene]piperidine-1-carboxylate**

tert-Butyl 4-oxopiperidine-1-carboxylate (2.0 g, 10 mmol) and cyclopropylacetonitrile (0.97 g, 12 mmol) were dissolved in THF (20 mL), heated to reflux, and allowed to stir for 3 hours. The mixture was then cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by MPLC on silica gel to afford the title compound as a white solid. LRMS (ESI) calc'd for $C_{15}H_{23}N_2O_2$ $[M+H]^+$ 263, Found 263.

Scheme #20

Intermediate #33



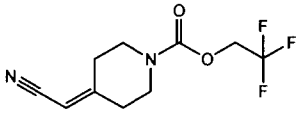
Step A-B. **[1-(Ethylsulfonyl)azetidin-3-ylidene]acetonitrile**

tert-Butyl 3-(cyanomethylidene)azetidine-1-carboxylate (5.0 g, 26 mmol) was dissolved in 4M HCl in dioxane (25.7 mL) and allowed to stir at ambient temperature for 16 hours. The mixture was concentrated to dryness *in vacuo*, then dissolved in DCM (30.0 mL) and cooled to -10 °C. DIPEA (11.6 g, 90.0 mmol) was added followed by ethanesulfonyl chloride (5.0 g, 39 mmol). The resulting mixture was allowed to stir for 7 hours before the mixture was

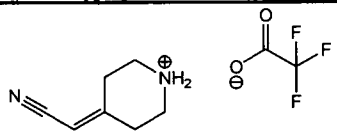
diluted with water and extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 5-70% EtOAc/heptane). Desired fractions were identified, combined, and concentrated *in vacuo* to afford the title compound. LRMS (ESI) calc'd for $C_7H_{10}N_2O_2S$ $[M+H]^+$: 187, Found: 187.

Scheme #20

Intermediate #34



2,2,2-Trifluoroethyl 4-(cyanomethylene)piperidine-1-carboxylate



Step A. **4-(Cyanomethylidene)piperidinium trifluoroacetate**

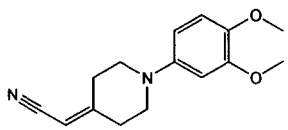
tert-Butyl 4-(cyanomethylene)piperidine-1-carboxylate (5.0 g, 22 mmol) was dissolved in DCM (75.0 mL). TFA (8.70 mL, 112 mmol) was added, and the resulting mixture was allowed to stir at ambient temperature for 2 hours. The mixture was concentrated *in vacuo* to afford the title compound. LRMS (ESI) calc'd for $C_7H_{10}N_2$ $[M+H]^+$: 123, Found: 123.

Step B. **2,2,2-Trifluoroethyl 4-(cyanomethylene)piperidine-1-carboxylate**

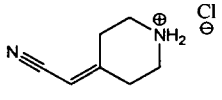
2,2,2-Trifluoroethanol (1.6 mL, 22 mmol) and TEA (6.2 mL, 45 mmol) were dissolved in MeCN (200 mL). N,N-disuccinimidyl carbonate (8.6 g, 34 mmol) was added and the resulting mixture was stirred at ambient temperature for 90 minutes. 4-(cyanomethylidene)piperidinium trifluoroacetate (5.3 g, 23 mmol) in DMSO (10 mL) was then added, followed by TEA (6.2 mL, 45 mmol). The resulting mixture was stirred at 50 °C for 16 hours. The reaction mixture was cooled to ambient temperature, diluted with EtOAc and washed sequentially with saturated aqueous $NaHCO_3$ and water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 0-5% MeOH/DCM) to afford the title compound. LRMS (ESI) calc'd for $C_{10}H_{11}F_3N_2O_2$ $[M+H]^+$: 249, Found: 249.

Scheme #20

Intermediate #35-1



[1-(3,4-Dimethoxyphenyl)piperidin-4-ylidene]acetonitrile



Step A: **4-(Cyanomethylidene)piperidinium chloride**

tert-Butyl 4-(cyanomethylidene)piperidine-1-carboxylate (20 g, 90 mmol) was dissolved in 4M HCl in dioxane and allowed to stir at ambient temperature for 2 hours. The mixture was then concentrated *in vacuo* to afford the title compound.

LRMS (ESI) calc'd for $C_7H_{10}N_2$ $[M+H]^+$: 123, Found: 123.

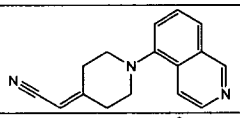
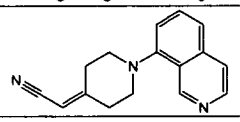
Step B: **[1-(3,4-Dimethoxyphenyl)piperidin-4-ylidene]acetonitrile**

In a sealed tube, 4-(cyanomethylidene)piperidinium chloride (16 mg, 0.10 mmol), $Pd_2(dba)_3$ (14 mg, 0.015 mmol), X-Phos (20 mg, 0.020 mmol), 4-bromo-1,2-dimethoxybenzene (33 mg, 0.15 mmol), and Cs_2CO_3 (98 mg, 0.30 mmol) were suspended in *t*-BuOH (0.5 mL). The reaction mixture was purged with argon for 5 minutes, the reaction flask was capped, and heated to 90 °C for 12 hours. The reaction was then cooled to ambient temperature and diluted with DMF/MeCN (1.0 mL, 50:50). To this mixture, Silica Supported-DMT (0.50 mmol, 0.57 mmol/g) followed by Silica Supported-Isocyanate (0.15 mmol, 1.33 mmol/g) was added. The resulting mixture was then shaken at 50 °C for 4 hours. The mixture was then passed through a nylon syringe filter (0.45 μm), and the filtrate was concentrated *in vacuo* to afford the title compound. The crude residue was used without further purification.

LRMS (ESI) calc'd for $C_{15}H_{18}N_2O_2$ $[M+H]^+$: 259, Found: 259.

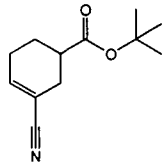
TABLE 5 depicts intermediates **35-2** through **35-3** that were prepared according to **Scheme #20** following similar procedures described for **Intermediates #35-1**, which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 5:

Interme -diate	Structure	Compound Name	Exact Mass $[M+H]^+$
35-2		[1-(isoquinolin-5-yl)piperidin-4-ylidene]acetonitrile	Calc'd 250, Found 250
35-3		[1-(isoquinolin-8-yl)piperidin-4-ylidene]acetonitrile	Calc'd 250, Found 250

Scheme #21

Intermediate #36-1



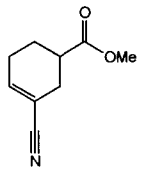
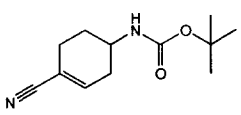
***tert*-Butyl 3-cyanocyclohex-3-ene-1-carboxylate**

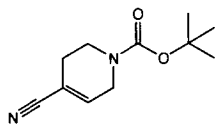
Step A-C: *tert*-Butyl 3-cyanocyclohex-3-ene-1-carboxylate

tert-Butyl 3-oxocyclohexanecarboxylate (1.35 g, 6.81 mmol) was taken up in water (11.4 mL) and stirred at ambient temperature. Sodium metabisulfite (0.75 g, 3.9 mmol) was added and the mixture was allowed to stir for 40 minutes. Diethyl ether (11.4 mL) was added, followed by potassium cyanide (0.70 g, 11 mmol). The resulting mixture was allowed to stir vigorously for 1 hour before it was partitioned between diethyl ether and water. The organic layer was washed with water, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue, used without further purification, was dissolved in DCM (22.0 mL). DIPEA (1.07 g, 8.26 mmol) was added and the resulting mixture was cooled to 0 °C. Methanesulfonyl chloride (0.69 g, 6.1 mmol) was added dropwise and the resulting mixture was maintained at 0 °C for 20 minutes then allowed to warm to ambient temperature. The mixture was partitioned between DCM and water. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue, used without further purification, was dissolved in pyridine (13.6 mL) and heated to 95 °C for 20 hours. The mixture was then allowed to cool to ambient temperature and was concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 0-45% EtOAc/hexanes). Desired fractions were identified, combined, and concentrated *in vacuo* to afford the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.63-6.58 (m, 1H), 2.54-2.48 (m, 1H), 2.44-2.40 (m, 2H), 2.36-2.16 (m, 2H), 2.02-1.94 (m, 1H), 1.71-1.63 (m, 1H), 1.44 (s, 9H).

TABLE 6 depicts intermediates **36-2** through **36-4** that were prepared according to **Scheme #21** following similar procedures described for **Intermediate #36-1**, which can be achieved by those of ordinary skill in the art of organic synthesis.

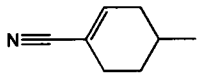
TABLE 6:

Interme-diate	Structure	Compound Name	^{1}H NMR δ (ppm)
36-2		methyl 3-cyanocyclohex-3-ene-1-carboxylate	^{1}H NMR (500 MHz, $CDCl_3$): δ 6.66-6.60 (m, 1H), 3.70 (s, 3H), 2.68-2.60 (m, 1H), 2.52-2.44 (m, 2H), 2.40-2.18 (m, 2H), 2.10-2.00 (m, 1H), 1.80-1.66 (m, 1H).
36-3		4-*tert*-butyl (4-cyanocyclohex-3-en-1-yl)carbamate	^{1}H NMR (600 MHz, $CDCl_3$): δ 6.53-6.50 (m, 1H), 4.46 (s, 1H), 3.77 (s, 1H), 2.58 (br d, J = 19.9 Hz, 1H), 2.48 – 2.27 (br d, J = 19.2 Hz, 2H), 2.03 (ddq, J = 19.3, 8.0, 3.6, 1H), 1.96-1.91 (m, 1H), 1.63–1.56 (m, 1H), 1.42 (s, 9H).

36-4		*tert*-butyl 4-cyano-3,6-dihydropyridine-1(2*H*)-carboxylate	^{1}H NMR (500 MHz, $CDCl_3$): δ 6.55 (br s, 1H), 4.05 (m, 2H), 3.55 (t, J = 5.6 Hz, 2H), 2.34 (br s, 2H), 1.46 (s, 9H).

Scheme #21

Intermediate #37-1



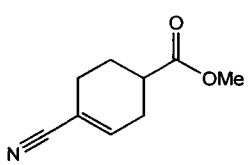
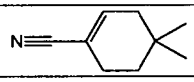
4-Methylcyclohex-1-ene-1-carbonitrile

Step A-B: **4-Methylcyclohex-1-ene-1-carbonitrile**

4-Methylcyclohexanone (1.0 g, 8.9 mmol) was added to a stirred solution of water (8.9 mL) containing sodium metabisulfite (0.98 g, 5.2 mmol). The resulting mixture was allowed to stir at ambient temperature for 15-30 minutes before diethyl ether (8.9 mL) was added followed by potassium cyanide (0.91 g, 14 mmol). The biphasic mixture was stirred vigorously for at least 30 minutes before the layers were partitioned and the organic layer was washed with water, followed by brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* (23 °C water bath) to afford 4-methyl -1-hydroxycyclohexanecarbonitrile as a crude residue, which was carried forward without further purification. The crude residue (0.50 g, 3.6 mmol) was combined with pyridine (18.3 mL, 226 mmol), and $POCl_3$ (1.34 mL, 14.4 mmol) in a microwave vial and sealed. The reaction mixture was heated to reflux for 16 hours. The reaction mixture was then cooled to ambient temperature, diluted with diethyl ether, and washed with 2N aqueous HCl saturated with sodium chloride (3x). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* (23 °C water bath) to afford the title compound as an oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.59-6.56 (m, 1H), 2.28–2.20 (m, 3H), 1.80–1.71 (m, 2H), 1.71–1.59 (m, 1H), 1.28-1.21 (m, 1H), 0.96 (d, J = 6.6, 3H).

TABLE 7 depicts intermediates **37-2** and **37-3** were prepared according to **Scheme #21** following similar procedures described for **Intermediate #37-1**, which can be achieved by those of ordinary skill in the art of organic synthesis.

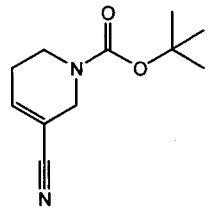
TABLE 7:

Interme-diate	**Structure**	**Compound Name**	^{1}H NMR **δ (ppm)**
37-2		methyl 4-cyanocyclohex-3-ene-1-carboxylate	^{1}H NMR (600 MHz, $CDCl_3$): δ 6.61-6.57 (m, 1H), 3.68 (s, 3H), 2.62-2.54 (m, 1H), 2.48-2.40 (m 2H), 2.36-2.22 (m, 2H), 2.10-2.02 (m, 1H), 1.80-1.70 (m, 1H).
37-3		4,4-	^{1}H NMR (600 MHz, $CDCl_3$): δ 6.55-6.52 (m, 1H), 2.24-

		dimethylcyclohex-1-ene-1-carbonitrile	2.19 (m, 2H), 1.96-1.91 (m, 2H), 1.41 (t, J = 6.4, 2H), 0.91 (s, 6H).

Scheme #22

Intermediate #38

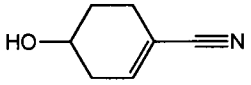


Steps A-B.: ***tert*-Butyl 5-cyano-3,6-dihydropyridine-1(2*H*)-carboxylate**

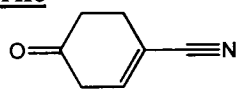
A solution of *n*-butyllithium (2.8 mL, 7.0 mmol, 2.5 M in hexanes) was added to a solution of diisopropylamine (1.0 mL, 7.0 mmol) in THF (10.0 mL) at –78 °C. The cooling bath was removed for 15 minutes, and then the reaction mixture was cooled back to –78 °C. A solution of *tert*-butyl 3-oxopiperidine-1-carboxylate (1.0 g, 5.0 mmol) in THF (6 mL) was added to the cooled solution of LDA dropwise over 5 minutes, maintained for 15 minutes, and then *N*-(5-chloropyridin-2-yl)-1,1,1-trifluoro-*N*-[(trifluoromethyl)sulfonyl]methanesulfonamide (2.4 g, 6.0 mmol) was added in one portion. The reaction mixture was stirred at –78 °C for 15 minutes, and then the cooling bath was removed. The reaction mixture was stirred for 45 minutes after removal of the cooling bath, and was then partitioned between EtOAc and water. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel (using a gradient elution of 0-20%, diethyl ether/hexanes) to afford *tert*-butyl 5-{[(trifluoromethyl)sulfonyl]oxy}-3,6-dihydropyridine-1(2*H*)-carboxylate as the second regioisomer to elute. A portion of the product (123 mg, 0.371 mmol) was combined with zinc cyanide (52 mg, 0.45 mmol), $Pd(PPh_3)_4$ (64 mg, 0.056 mmol) and DMF (1.9 mL) in a microwave tube. The reaction mixture was heated in the microwave at 100 °C for 20 minutes. After cooling to 23 °C, the reaction mixture was partitioned between EtOAc and water. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel (using a gradient elution of 0-100%, EtOAc/hexanes) to afford the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 (br s, 1H), 4.02 (br s, 2H), 3.49 (t, J = 5.6 Hz, 2H), 2.29 (br s, 2H), 1.47 (s, 9H).

Scheme #23

Intermediate #39



4-Hydroxycyclohex-1-ene-1-carbonitrile



Step A: **4-Oxocyclohex-1-ene-1-carbonitrile**

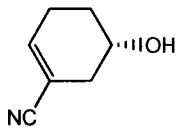
In a sealed tube, {[(3E)-4-methoxybuta-1,3-dien-2-yl]oxy}(trimethyl)silane (5.65 mL, 29.0 mmol) and acrylonitrile (1.91 mL, 29.0 mmol) were combined in benzene (9.67 mL), heated to reflux, and allowed to stir for 16 hours. The reaction mixture was then cooled to ambient temperature and the volatiles were removed *in vacuo* (23 °C water bath). The residue was stirred into a mixture of 1N aqueous HCl (29.0 mL, 29.0 mmol) and THF (9.7 mL). After being stirred at ambient temperature for 3 hours, the reaction mixture was extracted with diethyl ether. The organic layer was washed with de-ionized water (2x), brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* (23 °C water bath). The residue was purified by MPLC on silica gel (using a gradient elution of 0-50% hexanes/acetone). Desired fractions were identified, combined and concentrated *in vacuo* (23 °C water bath) to afford the title compound. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.68 (tt, J = 4.0, 1.5, 1H), 3.05 (dt, J = 4.3, 2.2, 2H), 2.71 (tq, J = 6.9, 1.9, 2H), 2.61–2.53 (t, J = 6.9 2H).

Step B: **4-Hydroxycyclohex-1-ene-1-carbonitrile**

To a stirred solution of 4-oxocyclohex-1-ene-1-carbonitrile (170 mg, 1.40 mmol) in MeOH (2.3 mL) at -78 °C was added cerium (III) chloride (484 mg, 1.96 mmol) in MeOH (4.7 mL). The resulting mixture was allowed to stir for 5 minutes at -78 °C before $NaBH_4$ (48 mg, 1.3 mmol) was added in one portion. The mixture was stirred for 20 minutes and then allowed to warm to ambient temperature. After being stirred for 30 minutes, the reaction mixture was diluted with water and extracted with diethyl ether (3x). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* (23 °C water bath) to afford the title compound. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.50 (tt, J = 3.9, 1.8, 1H), 4.03-3.98 (m, 1H), 3.50 – 3.42 (qd, J = 11.4, 4.5, 1H), 2.50 (br d, J = 19.2, 1H), 2.46–2.38 (m, 1H), 2.33–2.23 (m, 1H), 2.21–2.13 (m, 1H), 1.90–1.84 (m, 1H), 1.76–1.67 (m, 1H).

Scheme #24

Intermediate #40



(R or S)-5-Hydroxycyclohex-1-enecarbonitrile

Step A: **(R or S)-3-Cyanocyclohex-3-en-1-yl propionate**

To a 2L flask containing racemic 5-hydroxycyclohex-1-ene-1-carbonitrile (151 g, 1.22 mol), vinyl propionate (147 g, 1.47 mol), and MTBE (1.5 L) was added the enzyme AMANO Lipase PS from Burlholderiacepacia (20 g , Sigma-Aldrich). The mixture was stirred at ambient temperature for 48 hours. The mixture was filtered through celite and rinsed with

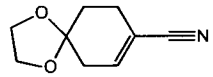
MTBE. The filtrate was concentrated *in vacuo* to remove both solvent and unreacted vinyl propionate. The residue was diluted with brine (1.5 L) and extracted with hexanes (1000mL +600mL x3 respectively). The combined organics was washed with H_2O (400 mL x5), then dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford the title compound, which was used without further purification.

Step B: **(R or S)-5-Hydroxycyclohex-1-enecarbonitrile**

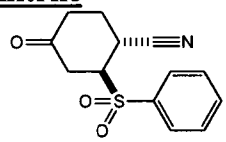
To a solution of (R or S)-3-cyanocyclohex-3-en-1-yl propanoate (210 g, 1.17 mol) in 1:1 THF/EtOH (2L) at 0 °C was added 3M aqueous NaOH (586 mL, 1.76 mol) dropwise via addition funnel over 30 minutes. After addition, The mixture was stirred at ambient temperature for 2 hours. The mixture was carefully neutralized with 3N aqueous HCl (195mL), concentrated to remove most of the THF/EtOH. The resulting mixture was diluted with brine (1.5 L) and extracted with EtOAc (1.2 L, then 600 mL x 4). The combined organics were washed with brine (200 mL x2). The aqueous layer was back-extracted with EtOAc (200 mL x 2), and the combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give the enantioenriched title compound (chiral HPLC: 98.4%ee). ^1H NMR data was consistent with that reported in the literature for racemic 5-Hydroxycyclohex-1-enecarbonitrile.

Scheme #25

Intermediate #41



1,4-Dioxaspiro[4.5]dec-7-ene-8-carbonitrile



Step A-C: **(1R,2S and 1S,2R)-4-Oxo-2-(phenylsulfonyl)cyclohexanecarbonitrile**

Benzenesulfinic acid sodium salt (9.4 g, 57 mmol) was dissolved in a mixture of water (18.3 mL) and acetic acid (9.1 mL). 2-Chloroprop-2-enenitrile (4.6 mL, 57 mmol) was added, followed by MeOH (18.3 mL). The resulting mixture was allowed to stir for 10 minutes before the solid product was collected by filtration and rinsed with minimal water. The majority of the solid filtered through with the rinse and so all material was rinsed through the filter. The filtrate was extracted with DCM (2x) and the combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford 2-chloro-3-(phenylsulfonyl)propanenitrile as a crude residue. Crude 2-chloro-3-(phenylsulfonyl)propanenitrile (6.1 g, 27 mmol) was dissolved in chloroform (41 mL) cooled in an ice-salt bath and stirred before adding TEA (3.7 mL, 27 mmol) dropwise. The mixture was allowed to stir at 0 °C for 20 minutes. The reaction mixture was then washed sequentially with dilute 1N aqueous HCl, followed by saturated aqueous $NaHCO_3$. The organic layer was dried

over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* (23 °C water bath) to afford (2E and 2Z)-3-(phenylsulfonyl)prop-2-enenitrile as a crude residue. This crude residue (4.9 g, 25.5 mmol) and (buta-1,3-dien-2-yloxy)(trimethyl)silane (4.2 g, 29.3 mmol) were refluxed together in benzene (63.8 mL) under nitrogen for 16 hours. The reaction mixture was then concentrated *in vacuo* to afford an oily mixture of intermediate adducts. The residue was dissolved in aqueous acetic acid (80%) and allowed to stir. After 1 hour at ambient temperature, the mixture was diluted with water and extracted with DCM (2x). The combined organic extracts were concentrated *in vacuo* and the residue was dissolved in DCM. A solid precipitated from the solution and was collected by filtration to afford the title compound.

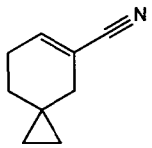
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.91 (d, J = 7.7, 2H), 7.74 (t, J = 7.4, 1H), 7.63 (t, J = 7.8, 2H), 3.81 (q, J = 4.4, 1H), 3.68 (q, J = 4.8, 1H), 2.76 (dd, J = 16.5, 6.3, 1H), 2.74 – 2.66 (m, 1H), 2.62 (dd, J = 11.4, 4.5, 1H), 2.61-2.56 (m, 2H), 2.25 (dq, J = 14.3, 4.9, 1H).

Step D-E: **1,4-Dioxaspiro[4.5]dec-7-ene-8-carbonitrile**

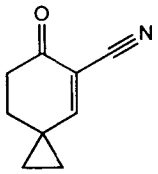
To a pressure vessel was added (1R,2S and 1S,2R)-4-oxo-2-(phenylsulfonyl) cyclohexanecarbonitrile (100 mg, 0.380 mmol), benzene (19.0 mL), ethylene glycol (0.9 mL, 15.6 mmol), and p-toluenesulfonic acid monohydrate (14 mg, 0.076 mmol). The vessel was capped and the reaction mixture was heated to reflux and allowed to stir for 16 hours. The reaction mixture was allowed to cool to ambient temperature before it was diluted with EtOAc. The organic layer was washed with water (3x), brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* (23 °C water bath) to afford (7S,8R and 7R,8S)-7-(phenylsulfonyl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile as a crude residue. To the crude residue (110 mg, 0.358 mmol) was added THF (7.1 mL) and potassium *tert*-butoxide (137 mg, 1.22 mmol). The reaction mixture was allowed to stir at ambient temperature for 15 minutes before it was diluted with diethyl ether. The organic layer was washed with water, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* (23 °C water bath) to afford the title compound.

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.48 (tt, J = 4.0, 1.8, 1H), 3.96 (s, 4H), 2.45 (tq, J = 6.6, 2.2, 2H), 2.39 (q, J = 3.1, 2H), 1.78 (t, J = 6.6, 2H).

Intermediate #42

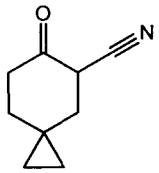


Spiro[2.5]oct-5-ene-5-carbonitrile



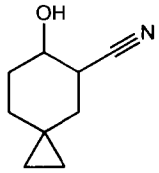
Step A: **6-Oxospiro[2.5]oct-4-ene-5-carbonitrile**

LDA (1.34 mL, 2.69 mmol, 2.0 M in hexanes) was combined with THF (2.4 mL) and cooled to -78 °C. To this mixture was added a solution of spiro[2.5]octan-6-one (0.30 g, 2.4 mmol) in THF (2.4 mL). The resulting mixture was stirred at -78 °C for 20 mins then taken up in a syringe and added to a mixture of tosyl cyanide (0.88 g, 4.8 mmol) in THF (2.4 mL) at -78 °C. The reaction mixture was allowed to stir at -78 °C for 45 mins then quenched with 0.5 M NaOH and extracted with EtOAc (2x) The combined organic extracts were washed with 1N aqueous HCl, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by MPLC on silica gel (using a gradient elution of 0-50% EtOAc/hexanes). Desired fractions were identified, combined and concentrated *in vacuo* to afford the title compound. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.02 (s, 1 H); 2.60-2.61 (m, 2 H); 1.96 (t, J = 7.0 Hz, 2 H); 1.19-1.21 (m, 4H).



Step B: **6-Oxospiro[2.5]octane-5-carbonitrile**

6-Oxospiro[2.5]oct-4-ene-5-carbonitrile (0.16 g, 1.1 mmol) was dissolved in MeOH (11 mL) and combined with 10 % palladium on activated carbon (0.12 g, 0.11 mmol). The resulting mixture was subjected to alternating vacuum and H_2 gas (4x). The mixture was then stirred under an atmosphere of H_2 (50 psi) for 16 hours. The mixture was then subjected to alternating vacuum and N_2 gas (4x). The mixture was filtered through celite and rinsed with MeOH. The filtrate was concentrated *in vacuo* to afford the title compound. The material was used without further purification.



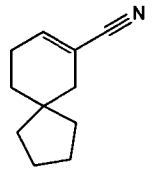
Step C: **6-Hydroxyspiro[2.5]octane-5-carbonitrile**

A solution of 6-oxospiro[2.5]octane-5-carbonitrile (130 mg, 0.87 mmol) in THF (4.3 mL) was stirred at ambient temperature and lithium borohydride (76 mg, 3.5 mmol) was added. The resulting mixture was stirred at ambient temperature for 16 hours. The mixture was diluted with water and extracted with EtOAc (2x). The combined organic extracts were washed with water, brine, dried over anhydrous Na2SO4, filtered, and concentrated *in vacuo* to afford the title compound. The material was used without further purification.

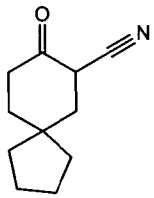
Step D: **Spiro[2.5]oct-5-ene-5-carbonitrile**

To a solution of 6-hydroxyspiro[2.5]octane-5-carbonitrile (110 mg, 0.73 mmol) in DCM (3.6 mL) was added DIPEA (190 mg, 1.4 mmol) followed by the dropwise addition of methanesulfonyl chloride (92 mg, 0.80 mmol). The resulting mixture was stirred at ambient temperature for 3 hours then DBU was added and stirring continued for 16 hours. The mixture was carefully diluted with water and extracted with EtOAc (2x). The combined organic extracts were washed with 1N aqueous HCl, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title compound. The residue was carried forward without further purification.

Intermediate #43



Spiro[4.5]dec-7-ene-7-carbonitrile



Step A: **8-Oxospiro[4.5]decane-7-carbonitrile**

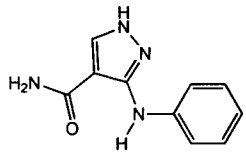
LDA (1.83 mL, 3.66 mmol, 2.0 M in hexanes) was combined with THF (3.2 mL) and cooled to -78 °C. To this mixture was added a solution of spiro[4.5]decan-8-one (0.50 g, 3.3 mmol) in THF (3.2 mL). The resulting mixture was stirred at -78 °C for 20 mins then taken up in a syringe and added to a mixture of tosyl cyanide (0.59 g, 3.3 mmol) in THF (3.2 mL) at -78 °C. The reaction mixture was allowed to stir at -78 °C for 45 mins then quenched with 0.5M NaOH and extracted with EtOAc (2x). The combined organic extracts were washed with 1N aqueous HCl, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by MPLC on silica gel (using a gradient elution of 0-50% EtOAc/hexanes). Desired fractions were identified, combined and concentrated *in vacuo* to afford the title compound. The residue was carried forward without further purification.

Step B: **Spiro[4.5]dec-7-ene-7-carbonitrile**

The title compound was prepared from 8-oxospiro[4.5]decane-7-carbonitrile according to **Steps C** and **D** for **Intermediate 42** (Spiro[2.5]oct-5-ene-5-carbonitrile). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.60-6.61 (m, 1 H); 2.21-2.22 (m, 2 H); 2.07 (d, J = 2.7 Hz, 2 H); 1.64-1.65 (m, 4 H); 1.49 (t, J = 6.3 Hz, 2 H); 1.38-1.41 (m, 4 H).

Scheme #26

Intermediate #44-1



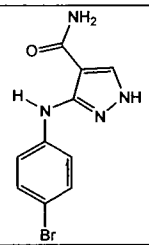
3-(Phenylamino)-1*H*–pyrazole-4-carboxamide

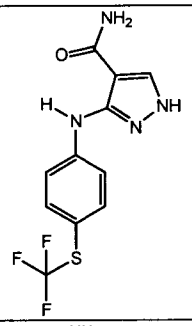
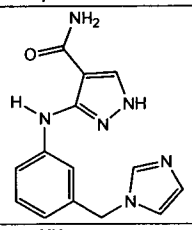
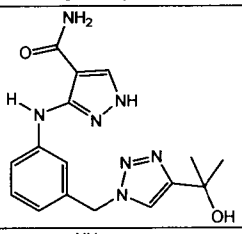
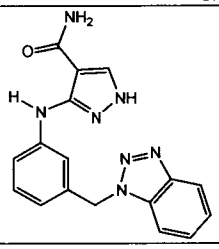
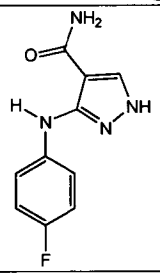
3-Amino-*1H*–pyrazole-4-carboxamide (19.8 g, 157 mmol), K_3PO_4 (66.7 g, 314 mmol), bromobenzene (23.2 mL, 220 mmol) and 2-propanol (785 mL) were combined in a round bottom flask and purged with a stream of N_2 gas for 40 minutes. $Pd_2(dba)_3$ (1.80 g, 1.96 mmol) and 2-di-*t*-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-tri-*i*-propylbiphenyl (3.77 g, 7.85 mmol) were added and the reaction was purged for an additional 5 minutes. The reaction mixture was then heated to 80 °C and allowed to stir under a N_2 atmosphere for 12 hours. The mixture was then allowed to cool to ambient temperature for an additional 16 hours. The reaction mixture was diluted with EtOAc (300 mL) and filtered through celite (slowly). The celite was washed with EtOAc (300 mL) and the filtrate was concentrated *in vacuo* to afford an oil which was purified by MPLC on silica gel (using a gradient elution of 0-10% MeOH/DCM). The major, low rf product, was isolated to afford a reddish-brown oily solid. The brown solid was suspended in 40 mL of warm MeOH, cooled to ambient temperature, and water (40 mL) was added. The mixture was stirred for 30 minutes and filtered. The solid was suction dried for 16 hours to afford the title compound as a peach-colored solid.

LRMS (ESI) calc'd for $C_{10}H_{10}N_4O$ $[M+H]^+$: 203, Found: 203.

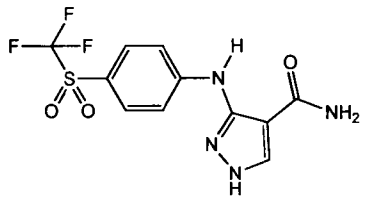
The following intermediates shown in **TABLE 8** were prepared according to **Scheme #26** following similar procedures described for **Intermediate #44-1**, which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 8:

Intermediate	Structure	Compound Name	Exact Mass $[M+H]^+$
44-2		3-[(4-bromophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 280, Found 280

44-3		3-({4-[(trifluoromethyl)sulfanyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 303, Found 303
44-4		3-{[3-(1*H*-imidazol-1-ylmethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 283, Found 283
44-5		3-[(3-{[4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl]methyl}phenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 342, Found 342
44-6		3-{[3-(1*H*-benzotriazol-1-ylmethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 334, Found 334
44-7		3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 221, Found 221

Intermediate #45



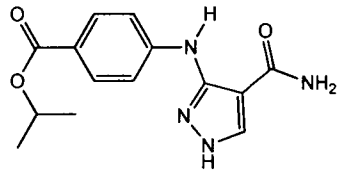
3-({4-[(Trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide

The title compound, **Intermediate #45**, can be prepared according to the general procedure described for **Intermediate #44-1** using 3-amino-*1H*–pyrazole-4-carboxamide (0.48 g, 3.8 mmol) and 1-bromo-4-[(trifluoromethyl)sulfonyl]benzene (1.0 g, 3.5 mmol) as starting materials. LRMS (ESI) calc'd for $C_{17}H_{18}FN_5O_2$ $[M+H]^+$: 335, Found: 335.

Alternatively, the title compound, **Intermediate #45,** can also be prepared by dissolving 3-({4-[(trifluoromethyl)sulfanyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide (0.50 g, 1.6 mmol) in acetic acid (5.0 mL) followed by the addition of hydrogen peroxide (0.87 mL, 9.9 mmol, 35 wt% in water). The resulting mixture was heated to 50 °C for 18 hours before additional hydrogen peroxide (0.87 mL, 9.9 mmol, 35 wt% in water) was added and the mixture was heated to 80 °C for 8 hours. The mixture was cooled to ambient temperature, concentrated *in vacuo* and diluted with EtOAc. The mixture was washed three times with aqueous sodium thiosulfate adjusted to pH>8 with saturated aqueous $NaHCO_3$. The organic layer was collected, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (eluting with 15% MeOH/DCM). Desired fractions were identified, combined, and concentrated *in vacuo* to afford the title compound. LRMS (ESI) calc'd for $C_{11}H_9F_3N_4O_3S$ $[M+H]^+$: 335, Found: 335.

Scheme #26

Intermediate #46

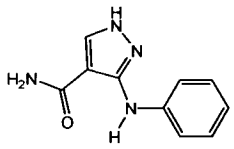


Propan-2-yl 4-[(4-carbamoyl-1*H*-pyrazol-3-yl)amino]benzoate

A round-bottomed flask was charged with 2-propanol (595 mL), and nitrogen was bubbled through the 2-propanol for 2 hours. $Pd_2(dba)_3$ (1.63 g, 1.78 mmol) and di-*tert*-butyl(2',4',6'-triisopropyl-3,4,5,6-tetramethylbiphenyl-2-yl)phosphine (3.43 g, 7.14 mmol) were added, and the mixture was stirred for 20 minutes. Potassium acetate (17.5 g, 178 mmol), 3-amino-1*H*-pyrazole-4-carboxamide (15.0 g, 119 mmol), and isopropyl 4-bromobenzoate (34.7 g, 143 mmol) were then added, and the reaction mixture was heated to 75 °C for 6.5 hours. The reaction mixture was then cooled to 23 °C, diluted with EtOAc (500 mL), and filtered through celite. The filtrate was adsorbed onto silica gel *in vacuo,* and purified by MPLC on silica gel (using a gradient elution of 30-90%, EtOAc/hexanes) to afford the title compound. LRMS (ESI) calc'd for $C_{14}H_{17}N_4O_3$ $[M+H]^+$: 289, Found: 289.

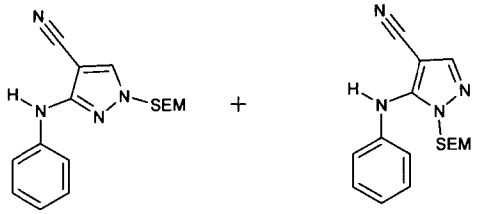
Scheme #27

Intermediate #44-1



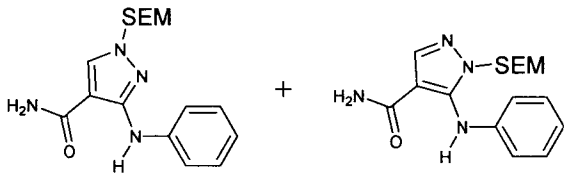
3-(Phenylamino)-1*H*-pyrazole-4-carboxamide

Intermediate #44-1 can be prepared by general methods described in **Scheme #26**, *vida* supra. Alternatively, **Intermediate 44-1** can also be prepared using the methods described below.



Step A: **3-(Phenylamino)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrazole-4-carbonitrile** *and* **5-(phenylamino)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrazole-4-carbonitrile**

To a microwave vessel was added a mixture of 3-amino-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrazole-4-carbonitrile (6.0 g, 25 mmol) 4-iodobenzene (3.38 mL, 30.2 mmol), dioxane (100 mL) and Cs_2CO_3 (25 g, 76 mmol). The mixture was degassed by bubbling nitrogen gas for 5 minutes. $Pd_2(dba)_3$ (3.46 g, 3.78 mmol), and X-Phos (0.60 g, 1.3 mmol) were then added, and the mixture was capped and heated to 120 °C. After heating for 16 hours, the mixture was allowed to cool to ambient temperature and was filtered through celite. The filtrate was adsorbed on silica gel *in vacuo* and the mixture was purified by MPLC on silica gel (using a gradient elution of 0-50% EtOAc/hexanes) to afford the title compounds. LRMS (ESI) calc'd for $C_{16}H_{22}N_4OSi$ $[M+H]^+$: 315, Found: 315.



Step B: **3-(Phenylamino)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrazole-4-carboxamide** *and* **5-(phenylamino)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrazole-4-carboxamide**

To a solution containing a mixture of 3-(phenylamino)-1-{[2-(trimethylsilyl)ethoxy]methyl}-*1H*-pyrazole-4-carbonitrile and 5-(phenylamino)-1-{[2-(trimethylsilyl)ethoxy]methyl}-*1H*-pyrazole-4-carbonitrile (2.46 g, 7.82 mmol) in DMSO (26.1 mL) and EtOH (52.2 mL) was added 5M aqueous NaOH (11.0 mL, 54.8 mmol) followed by the dropwise addition of 30% H_2O_2 (11.2 mL, 110 mmol). The mixture was maintained for 20 minutes before it was allowed to cool to ambient temperature. EtOAc (200mL) and water (100mL) were added and the layers partitioned. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford a crude mixture of the title compounds, which were used without further purification. LRMS (ESI) calc'd for C16H24N4O2Si $[M+H]^+$: 333, Found: 333. ^1H NMR (600 MHz, $CDCl_3$) δ 8.65 (s, 4H), 7.80 (s,

1H), 7.69 (s, 1H), 7.57 – 7.52 (m, 2H), 7.51-7.42 (m, 1H), 7.30 – 7.21 (m, 2H), 7.15-7.07 (m, 1H), 6.99 (t, J = 7.4, 2H), 6.92 – 6.81 (m, 2H), 5.54 (br s, 2H), 5.31 (s, 2H), 5.17 (s, 2H), 3.70 (dd, J = 9.0, 7.7, 2H), 3.50 – 3.40 (m, 2H), 0.99 – 0.90 (m, 2H), 0.84 – 0.78 (m, 2H), -0.01 - -0.03 (m, 9H), -0.05 - -0.07 (m, 9H).

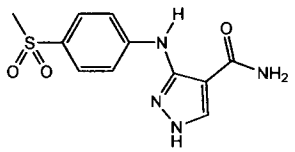
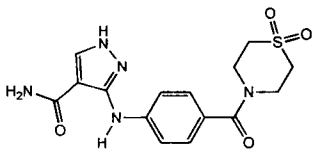
Step C: **3-(Phenylamino)-1*H*-pyrazole-4-carboxamide**

To a solution containing a mixture of 3-(phenylamino)-1-{[2-(trimethylsilyl)ethoxy]methyl}-*1H*-pyrazole-4-carbonitrile and 5-(phenylamino)-1-{[2-(trimethylsilyl)ethoxy]methyl}-*1H*-pyrazole-4-carbonitrile (2.6 g, 7.8 mmol) in EtOH (40.3 mL) was added 2N aqueous HCl (40.3 mL). The resulting mixture was heated at 0 °C for 1 hour. The mixture was cooled to ambient temperature and carefully neutralized with 3N aqueous Na_2CO_3 until pH ~9. The solution was further diluted with H_2O (400 mL), the layers were partitioned and the aqueous mixture was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was adsorbed on silica gel *in vacuo* and purified by MPLC on silica gel (using a gradient elution of 0-100% EtOAc/DCM) to afford the title compound, which was used without further purification.

LRMS (ESI) calc'd for $C_{10}H_{10}N_4O$ $[M+H]^+$: 202, Found: 203.

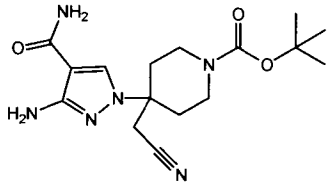
The following intermediates shown in **TABLE 9** were prepared according to **Scheme #27** following similar procedures described for **Intermediate #44-1**, which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 9:

Intermediate	Structure	Compound Name	Exact Mass $[M+H]^+$
44-8		3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 281, Found 281
44-9		3-({4-[(1,1-dioxidothiomorpholin-4-yl)carbonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 364, Found 364

Scheme #28

Intermediate #47-1



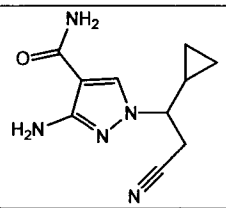
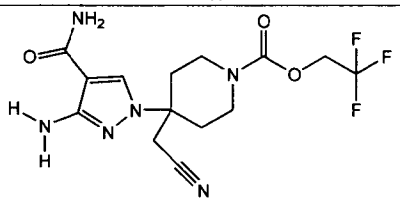
***tert*-Butyl 4-(3-amino-4-carbamoyl-1*H*-pyrazol-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate**

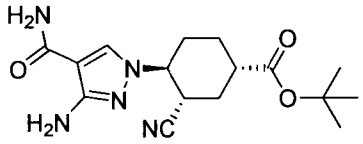
3-Amino-1*H*-pyrazole-4-carboxamide (0.80 g, 6.3 mmol) and *tert*-butyl 4-(cyanomethylene)piperidine-1-carboxylate (2.1 g, 9.5 mmol) were combined with MeCN (31 mL) in a pressure vessel. DBU (1.05 mL, 6.98 mmol) was then added at ambient temperature. The reaction vessel was sealed and the mixture was heated to 80 °C for 16 hours. The reaction mixture was then allowed to cool to ambient temperature before water (150 mL) was added. The aqueous mixture was extracted with EtOAc (2x). The organic layers were then combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was adsorbed on silica gel *in vacuo* and purified by MPLC on silica gel (using a gradient elution of 75-100% EtOAc/hexanes) to afford the title compound, **Intermediate #47-1**.

LRMS (ESI) calc'd for $C_{16}H_{24}N_6O_3$ $[M+H]^+$: 349, Found: 349

The following intermediates shown in **TABLE 10** were prepared according to **Scheme #28** following similar procedures described for **Intermediate #47-1**, which can be achieved by those of ordinary skill in the art of organic synthesis.

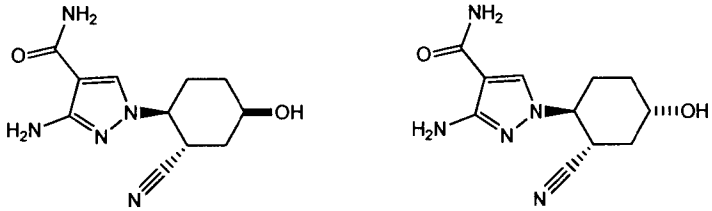
TABLE 10:

Intermediate	Structure	Compound Name	Exact Mass $[M+H]^+$
47-2		3-amino-1-(2-cyano-1-cyclopropylethyl)-1*H*-pyrazole-4-carboxamide	Calc'd 220, Found 220
47-3		2,2,2-trifluoroethyl 4-(3-amino-4-carbamoyl-1*H*-pyrazol-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate	Calc'd 375, Found 375

47-4		(1S,3S,4S and 1R,3R,4R)-tert-butyl 4-(3-amino-4-carbamoyl-1*H*-pyrazol-1-yl)-3-cyanocyclohexanecarboxylate	Calc'd 334, Found 334

Scheme #28

Intermediate #48-1 and 48-2



3-Amino-1-[(1S,2S,4R and 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide *and* **3-amino-1-[(1S,2S,4S and 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide**

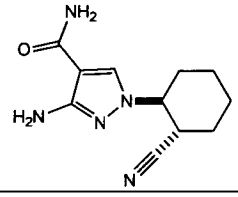
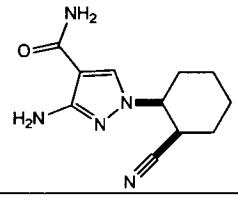
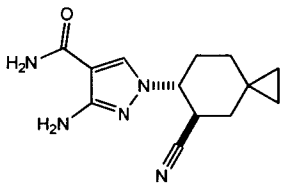
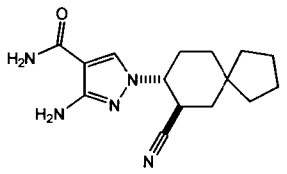
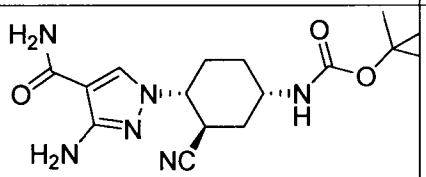
DBU (263 mL, 1.74 mol) was added to a mixture of 3-amino-1*H*-pyrazole-4-carboxamide (110 g, 872 mmol) and 5-hydroxycyclohex-1-ene-1-carbonitrile (161 g, 1.31 mol) in ethanol (1100 mL) at 23 °C. The reaction mixture was then heated to 70 °C for 16 hours. The mixture was then cooled to ambient temperature with stirring. The precipitates were filtered, washed with EtOH (150 mLx2), and dried under a nitrogen flow for 4 hours to afford the title compound. The stereochemistry of the major isomer was 1,2-trans, 1,4-cis, and the minor isomer was 1,2-trans, 1,4-trans, with a ratio of ~6:1.

Intermediate #48-1: Major isomer; 3-Amino-1-[(1S,2S,4R and 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide. LRMS (ESI) calc'd for $C_7H_{16}N_5O_2$ $[M+H]^+$: 250, Found: 250.

Intermediate #48-2: Minor isomer; 3-Amino-1-[(1S,2S,4S and 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide. LRMS (ESI) calc'd for $C_7H_{16}N_5O_2$ $[M+H]^+$: 250, Found: 250.

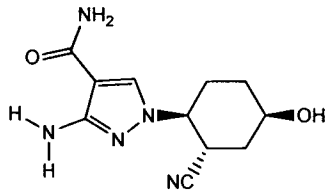
The following intermediates shown in **TABLE 11** were prepared according to **Scheme #28** following similar procedures described for **Intermediate #48-1** and **48-2**, which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 11:

Intermediate	Structure	Compound Name	Exact Mass $[M+H]^+$
48-3		3-Amino-1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 234, Found 234
48-4		3-amino-1-[(1S,2R and 1R,2S)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 234, Found 234
48-5		3-amino-1-((5R,6R)-5-cyanospiro[2.5]octan-6-yl)-1*H*-pyrazole-4-carboxamide	Calc'd 260, Found 260
48-6		3-amino-1-((7R,8R)-7-cyanospiro[4.5]decan-8-yl)-1*H*-pyrazole-4-carboxamide	Calc'd 287, Found 287
48-7		*tert*-Butyl [(1R,3S,4S and 1S,3R,4R)-4-(3-amino-4-carbamoyl-1*H*-pyrazol-1-yl)-3-cyanocyclohexyl]carbamate	Calc'd 349, Found 349

Scheme #24, 28 and 36

Intermediate #49



<u>3-Amino-1-((1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl)-1*H*-pyrazole-4-carboxamide</u>

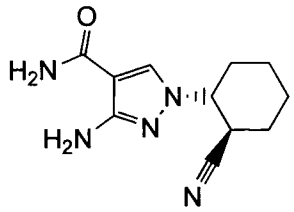
DBU (56.5 mL, 375 mmol) was added to a mixture of (R or S)-5-hydroxycyclohex-1-enecarbonitrile (**Intermediate #40,** 46.1 g, 375 mmol) and 3-amino-1*H*-

pyrazole-4-carboxamide (34 g, 270 mmol) in ethanol (346 mL) at 23 °C. The reaction vessel capped with a reflux condenser and heated at 75 °C. After stirring at 75 °C for 18 hours, the heating source was removed and stirring was continued for 4 hours. The suspended precipitate was filtered, and the solids were washed with two portions of ethanol (50 mL each). The solids were collected and dried under a flow of nitrogen for 16 hours to afford the title compound. ^{1}H NMR analysis indicated diastereomeric purity of >95%.

^{1}H NMR (500 MHz, CD_3OD) δ 7.98 (s, 1H), 4.15 (td, J = 11.5, 4.0 Hz), 4.09-4.06 (m, 1H), 3.59-3.54 (m, 1H), 2.33 (qd, J = 13.0, 3.6 Hz, 1H), 2.22 (dq, J = 13.7, 3.2 Hz, 1H), 1.98-1.88 (m, 2H), 1.82-1.76 (m, 1H), 1.73-1.66 (m, 1H).

LRMS (ESI) calc'd for $C_{11}H_{16}N_5O_2$ $[M+H]^+$: 250, Found: 250.

Intermediate #50-1 and 50-2



3-Amino-1-((1R,2R or 1S,2S)-2-cyanocyclohexyl)-1*H*-pyrazole-4-carboxamide

A racemic diastereomeric mixture of 3-amino-1-((1R,2R or 1S,2S)-2-cyanocyclohexyl)-1*H*-pyrazole-4-carboxamide, **Intermediate 48-3**, was chirally resolved to the constituent enantiomers by SFC chromatography (Chiral Technology IC-H 2.1 X 25cm, 5uM, 20% MeOH/CO_2). Desired fractions were identified, combined, and concentrated *in vacuo* to afford enantiomerically pure samples of the title compounds:

Example 50-1: 1st enantiomer to elute from column; 3-amino-1-((1R,2R or 1S,2S)-2-cyanocyclohexyl)-1*H*-pyrazole-4-carboxamide. LRMS (ESI) calc'd for $C_{11}H_{15}N_5O$ [M+H]+: 234, Found: 234.

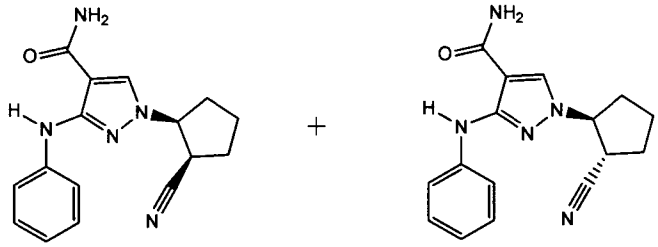
Example 50-2: 2nd enantiomer to elute from column; 3-amino-1-((1R,2R or 1S,2S)-2-cyanocyclohexyl)-1*H*-pyrazole-4-carboxamide. LRMS (ESI) calc'd for $C_{11}H_{15}N_5O$ [M+H]+: 234, Found: 234.

EXAMPLES OF THE INSTANT INVENTION

The following experimental procedures detail the preparation of specific examples of the instant invention. The examples are for illustrative purposes only and are not intended to limit the scope of the instant invention in any way.

Scheme #30

Example #1-1 and 1-2



1-{[(1S,2R) and (1R,2S)]-2-cyanocyclopentyl}-3-(phenylamino)-1*H*-pyrazole-4-carboxamide and **1-{[(1S,2S) and (1R,2R)]-2-cyanocyclopentyl}-3-(phenylamino)-1*H*-pyrazole-4-carboxamide**

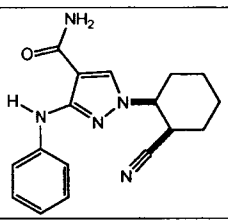
DBU (0.27 mL, 0.18 mmol) was added to a mixture of 3-(phenylamino)-1*H*-pyrazole-4-carboxamide (30 mg, 0.15 mmol) and cyclopent-1-ene-carbonitrile (21 mg, 0.22 mmol) in MeCN (0.74 mL). The vial was capped and allowed to stir at ambient temperature for 15 hours. The reaction mixture was taken up in DMSO (2mL) and purified by reverse-phase preparative HPLC (MeCN/water, with 0.1% v/v TFA modifier). Desired fractions were combined, basified with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic layer was dried over anhydrous $NaSO_4$, filtered, and concentrated *in vacuo* to afford the title compounds in a 1:1 cis/trans ratio.

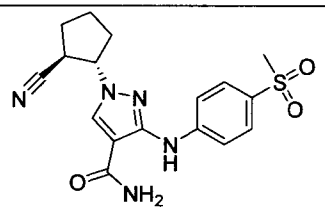
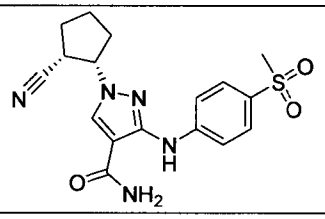
Example #1-1: ^{1}H NMR (600 MHz, cdcl3) δ 8.68 (s, 1H), 7.68 (s, 1H), 7.52 (dd, J = 1.0, 8.6, 2H), 7.29 – 7.25 (m, 2H), 6.88 (t, J = 7.3, 1H), 5.56 (s, 2H), 4.68 (q, J = 6.8, 1H), 3.26 (dd, J = 7.4, 14.2, 1H), 2.45 – 2.30 (m, 2H), 2.30 – 2.15 (m, 3H), 1.91 – 1.78 (m, 1H). LRMS (ESI) calc'd for $C_{16}H_{17}N_5O$ $[M+H]^+$: 296, Found: 296.

Example #1-2: ^{1}H NMR (600 MHz, cdcl3) δ 8.74 (s, 1H), 7.64 (s, 1H), 7.51 (d, J = 7.7, 2H), 7.27 (dd, J = 7.5, 8.4, 2H), 6.89 (t, J = 7.3, 1H), 5.67 (s, 2H), 4.59 (q, J = 7.7, 1H), 3.36 (q, J = 8.5, 1H), 2.43 – 2.27 (m, 2H), 2.27 – 2.16 (m, 1H), 2.15 – 1.97 (m, 2H), 1.97 – 1.87 (m, 1H). LRMS (ESI) calc'd for $C_{16}H_{17}N_5O$ $[M+H]^+$: 296, Found: 296.

The following examples shown in **TABLE 12** were prepared according to **Scheme #23** following similar procedures described for **Example #1-1**, which can be achieved by those of ordinary skill in the art of organic synthesis.

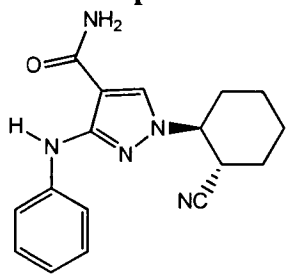
TABLE 12:

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
1-3		1-[(1S,2R and 1R, 2S)-2-cyanocyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 310, Found 310

1-4		1-{[(1S,2S) and (1R,2R)-2-cyanocyclopentyl]}-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 374, found 374
1-5		1-{[(1S,2R) and (1R, 2S)]-2-cyanocyclopentyl]}-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 374, found 374

Scheme #30

Example #2-1

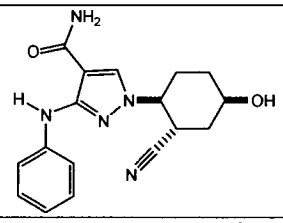
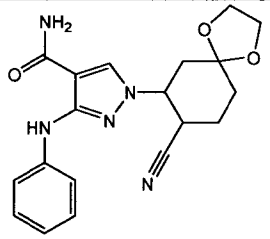
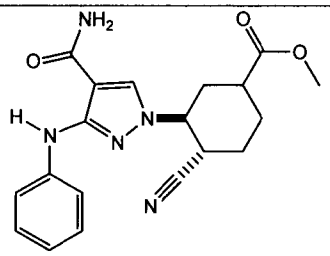
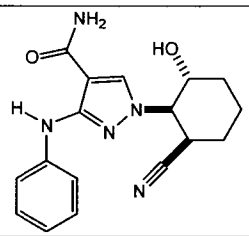
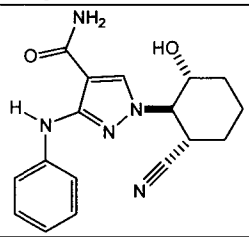
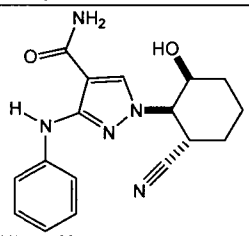


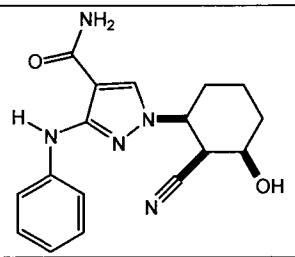
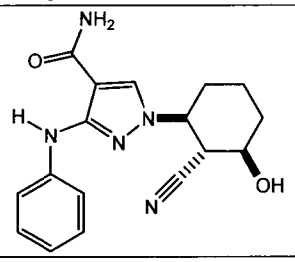
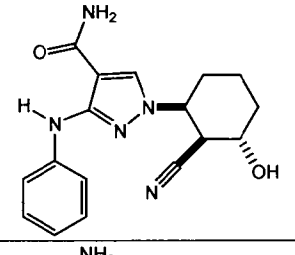
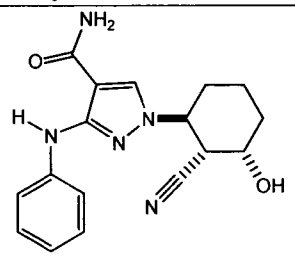
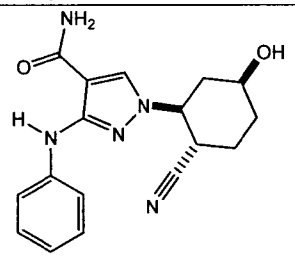
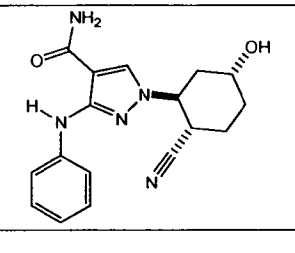
1-((1S,2S and 1R,2R)-2-cyanocyclohexyl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide

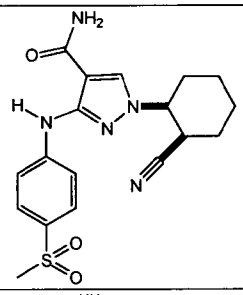
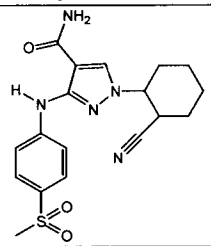
DBU (0.37 mL, 2.4 mmol) was added to a mixture of 3-(phenylamino)-1*H*-pyrazole-4-carboxamide (**Intermediate 44-1**, 200 mg, 0.989 mmol) and cyclohex-1-enecarbonitrile (1.12 mL, 9.90 mmol) in DMF (4.9 mL). The reaction vessel was sealed, and the reaction mixture was heated to 120 °C for 4 hours. The reaction mixture was then cooled to ambient temperature and partitioned between EtOAc and water. The organic layer was washed with brine, the washed solution was dried over anhydrous sodium sulfate, and the dried solution was filtered. The filtrate was concentrated *in vacuo* and purified by MPLC on silica gel (using a gradient elution of 60 to 100% EtOAc/hexanes) to afford the title compound. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.72 (s, 1H), 7.61 (s, 1H), 7.52 (d, J = 7.8 Hz, 2H), 7.27 (t, J = 7.8 Hz, 2H), 6.88 (t, J = 7.2 Hz, 1H), 5.38 (br s, 2H), 3.94 (td, J = 11.1, 4.2 Hz, 1H), 3.22-3.17 (m, 1H), 2.31-2.28 (m, 1H), 2.18-2.06 (m, 2H), 1.98-1.94 (m, 1H), 1.88-1.83 (m, 1H), 1.70 (qd, J = 13, 3.9 Hz, 1.44-1.38 (m, 2H). LRMS (ESI) calc'd for $C_{17}H_{20}N_5O$ $[M]^+$: 310, Found: 310.

The following examples shown in **TABLE 13** were prepared according to **Scheme #23** following similar procedures described for **Examples #2-1**, which can be achieved by those of ordinary skill in the art of organic synthesis.

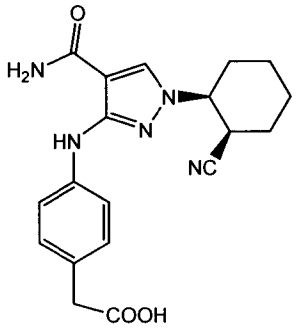
TABLE 13:

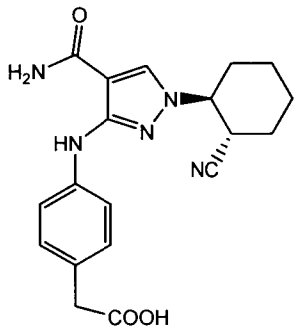
Example	Structure	Compound Name	Exact Mass [M+H]+
2-2		1-[(1S,2S,4R and 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 326, Found 326
2-3		1-(8-cyano-1,4-dioxaspiro[4.5]dec-7-yl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 368, Found 368
2-4		methyl (3R,4R and 3S,4S)-3-[4-carbamoyl-3-(phenylamino)-1*H*-pyrazol-1-yl]-4-cyanocyclohexanecarboxylate	Calc'd 368, Found 368
2-5		1-[(1R,2R,6R and 1S,2S,6S)-2-cyano-6-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 326, Found 326
2-6		1-[(1R,2S,6R and 1S,2R,6S)-2-cyano-6-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 326, Found 326
2-7		1-[(1R,2S,6S and 1S,2R,6R)-2-cyano-6-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 326, Found 326

Example	Structure	Compound Name	Exact Mass [M+H]+
2-8		1-[(1S,2R,3R and 1R,2S,3S)-2-cyano-3-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 326, Found 326
2-9		1-[(1S,2S,3R and 1R,2R,3S)-2-cyano-3-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 326, Found 326
2-10		1-[(1S,2R,3S and 1R,2S,3R)-2-cyano-3-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 326, Found 326
2-11		1-[(1S,2S,3S and 1R,2R,3R)-2-cyano-3-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 326, Found 326
2-12		1-[(1R,2R,5R and 1S,2S,5S)-2-cyano-5-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 326, Found 326
2-13		1-[(1S,2S,5R and 1R,2R,5S)-2-cyano-5-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 326, Found 326

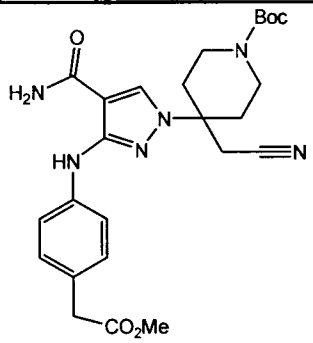
Example	Structure	Compound Name	Exact Mass [M+H]+
2-14		1-[(1S,2R and 1R,2S)-2-cyanocyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 388, Found 388
2-15		1-(2-cyanocyclohexyl)-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 388, Found 388

Example # 3-1 and 3-2



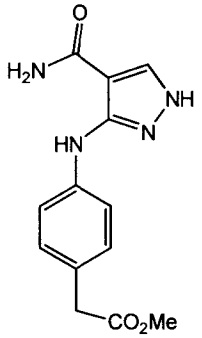


[4-({4-Carbamoyl-1-[(1S,2R and 1R,2S)-2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]acetic acid and **[4-({4-carbamoyl-1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]acetic acid**



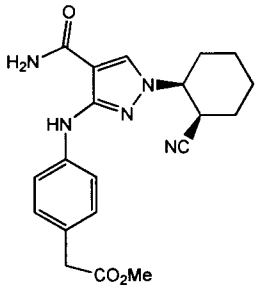
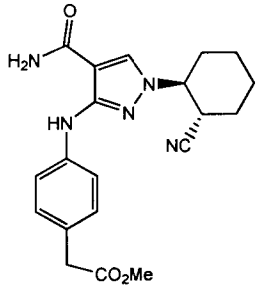
Step A: ***tert*-Butyl 4-(4-carbamoyl-3-{[4-(2-methoxy-2-oxoethyl)phenyl]amino}-1*H*-pyrazol-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate**

To a microwave vessel was added *tert*-butyl 4-(3-amino-4-carbamoyl-1*H*-pyrazol-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate (**Intermediate 47-1**, 0.30 g, 0.86 mmol), KOAc (127 mg, 1.29 mmol), methyl (4-bromophenyl)acetate (237 mg, 1.03 mmol) and 2-propanol (4.3 mL). The mixture was degassed for 5 minutes by bubbling argon gas. $Pd_2(dba)_3$ (39 mg, 0.04 mmol) and 2-di-t-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-tri-i-propylbiphenyl (83 mg, 0.17 mmol) were added, the vial was sealed and heated at 95 °C for 18 hours. The mixture was cooled to ambient temperature, then diluted with EtOAc and washed with H_2O. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 50-100% EtOAc/hexanes) to afford the title compound. ^{1}H NMR (600 MHz, Acetone-d_6): δ 9.17 (s, 1H), 8.45 (s, 1H), 7.52-7.55 (m, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.14 (brs, 1H), 6.51 (brs, 1H), 3.80-3.90 (m, 2H), 3.60 (s, 3H), 3.53 (s, 2H), 3.15 (s, 2H), 3.00-3.18 (m, 2H), 2.52-2.60 (m, 2H), 2.04-2.12 (m, 2H), 1.42 (s, 9H). LRMS (ESI) calc'd for $C_{16}H_{25}N_6O_3$ $[M+H]^+$: 497, Found: 497



Step B: **Methyl {4-[(4-carbamoyl-1*H*-pyrazol-3-yl)amino]phenyl}acetate**

To a solution of *tert*-Butyl 4-(4-carbamoyl-3-{[4-(2-methoxy-2-oxoethyl)phenyl]amino}-1*H*-pyrazol-1-yl)-4-(cyanomethyl)piperidine-1-carboxylate (226 mg, 0.46 mmol) in THF (2.3 mL) at 0 °C was added KO^{t}Bu (0.68 mL, 0.68 mmol, 1.0M in THF), and the mixture was stirred at 0 °C for 20 minutes, then ambient temperature for 20 minutes. The mixture was diluted with saturated aqueous NH_4Cl, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Et_2O (5 mL) was added to the resulting oily residue and a solid precipitated out. This solid was collected by decant, and washed with Et_2O to afford the title compound. LRMS (ESI) calc'd for $C_{13}H_{15}N_4O_3$ [M+H]+: 275, Found: 275

Step C: **Methyl [4-({4-carbamoyl-1-[(1S,2R and 1R,2S)-2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]acetate** and **methyl [4-({4-carbamoyl-1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]acetate**

To a solution methyl {4-[(4-carbamoyl-1*H*-pyrazol-3-yl)amino]phenyl}acetate (50 mg, 0.18 mmol) in EtOH (0.7 mL) was added 1-cyanocyclohexene (195 mg, 1.82 mmol) and DBU (0.055 mL, 0.37 mmol). The mixture was heated at 90 °C for 18 hours. The mixture was diluted with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The combined organics were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 0-10% MeOH/DCM) to afford the title compounds.

Example #3-1C: methyl [4-({4-carbamoyl-1-[(1S,2R and 1R,2S.)-2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]acetate. LRMS (ESI) calc'd for $C_{20}H_{24}N_5O_3$ [M+H]+: 396, Found: 396.

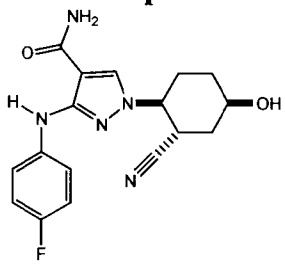
Example #3-2C: methyl [4-({4-carbamoyl-1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]acetate. LRMS (ESI) calc'd for $C_{20}H_{24}N_5O_3$ [M+H]+: 396, Found: 396.

Step D: **[4-({4-carbamoyl-1-[(1S,2R and 1R,2S)-2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]acetic acid** and **[4-({4-carbamoyl-1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]acetic acid**

To a solution of methyl [4-({4-carbamoyl-1-[(1S,2R and 1R,2S)-2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]acetate (**Example #3-2C**, 5 mg, 0.01 mmol) in 1:1 MeOH/THF (1.0 mL) at ambient temperature was added a solution of LiOH (3.0 mg, 0.13 mmol) in H_2O (0.4 mL). The mixture was stirred at ambient temperature for 2 hours, acidified with 1N aqueous HCl to pH 3~4, diluted with H_2O, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to afford [4-({4-carbamoyl-1-[(1S,2R and 1R,2S)-2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]acetic acid, **Example #3-1**. ^1H NMR (600 MHz, acetone-d_6): δ 10.6 (brs, 1H), 9.18 (s, 1H), 8.21 (s, 1H), 7.54-7.55 (m, 2H), 7.04-7.23 (m, 3H), 6.42 (brs, 1H), 4.36 (dt, J= 12.6, 3.6 Hz, 1H), 3.83-3.84 (m, 1H), 2.22-2.25 (m, 1H), 2.09-2.13 (m, 1H), 2.00-2.05 (m, 2H), 1.86-1.94 (m, 2H), 1.74-1.79 (m, 1H), 1.56-1.62 (m, 1H). LRMS (ESI) calc'd for $C_{19}H_{22}N_5O_3$ $[M+H]^+$: 368, Found: 368

To a solution of methyl [4-({4-carbamoyl-1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]acetate (**Example #3-1C**, 16 mg, 0.040 mmol) in a mixture of 1:1 MeOH/THF (1.0 mL) was added a solution of LiOH (9.7 mg, 0.41 mmol) in H_2O (0.4mL). The mixture was stirred at ambient temperature for 2 hours. The mixture was acidified with 1N aqueous HCl to pH 3~4, diluted with H_2O, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by reverse phase preparative HPLC (using a gradient elution of 30-65% MeCN/H_2O containing 0.1% TFA). Desired fractions were collected, diluted with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford [4-({4-carbamoyl-1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]acetic acid, **Example #3-2**. ^{1}H NMR (600 MHz, acetone-d_6): δ 10.7 (brs, 1H), 9.19 (s, 1H), 8.17 (s, 1H), 7.31-7.54 (m, 2H), 7.02-7.20 (m, 3H), 6.46 (brs, 1H), 4.29 (td, J = 10.8 and 4.8 Hz), 3.34 (td, J = 10.8 and 4.8 Hz), 2.24-2.28 (m, 1H), 2.02-2.08 (m, 2H), 1.85-1.90 (m, 1H), 1.72-1.82 (m, 2H), 1.38-1.56 (m, 2H). LRMS (ESI) calc'd for $C_{19}H_{22}N_5O_3$ [M+H]+: 368, Found: 368

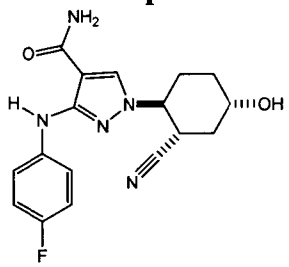
Example #4



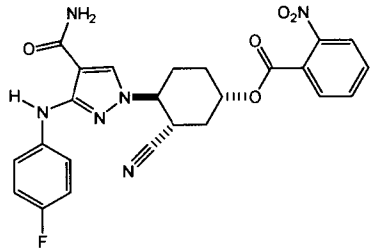
1-[(1S,2S,4R and 1R,2R,4S)-2-Cyano-4-hydroxycyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide

The title compound , **Example #4,** was prepared according to the general procedure describe for **Example #2-1** using 3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide (**Intermediate #44-7**, 1.0 g, 4.5 mmol) and 5-hydroxycyclohex-1-ene-1-carbonitrile (0.84 g, 6.8 mmol) as starting materials. ^{1}H NMR (DMSO-d_6): δ 9.11 (s, 1H), 8.25 (s, 1H), 7.63 (br s, 1H), 7.51 (m, 2H), 7.14 (br s, 1H), 7.08 (m, 2H), 4.88 (d, J = 2.5 Hz, 1H), 4.40 (ddd, J = 11.5, 11.5, 3.5 Hz, 1H), 3.95 (br s, 1H), 3.47 (ddd, J = 12.5, 12.5, 4 Hz, 1H), 2.19 (dddd, J = 12.5,12.5, 12.5, 3.5 Hz, 1H), 2.09 (br d, J = 12 Hz, 1H), 1.95 (br dd, J = 11.5, 11.5 Hz, 1H), 1.74 (m, 2H), 1.62 (br dd, J = 13.0, 13.0 Hz, 1H). LRMS (ESI) calc'd for $C_{17}H_{18}FN_5O_2$ [M+H]$^+$: 344, Found: 344.

Example #5



1-[(1S,2S,4S and 1R,2R,4R)-2-Cyano-4-hydroxycyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide



Step A: **1-[(1S,3S,4S and 1R,3R,4R)-4-{4-Carbamoyl-3-(4-fluorophenyl)amino}-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl 2-nitrobenzoate**

1-[(1S,2S,4R and 1R,2R,4S)-2-Cyano-4-hydroxycyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide (**Example #4**, 500 mg, 1.46 mmol) was dissolved in THF (7.9 mL) and cooled to 0 °C. Triphenylphosphine (1.15 g, 4.37 mmol), 2-nitrobenzoic acid (730 mg, 4.37 mmol) and diethyl azodicarboxylate (0.69 mL, 4.37 mmol) were added sequentially, and the reaction mixture was allowed to warm to ambient temperature for 16 hours. The reaction mixture was then partitioned between water and EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 50-100% EtOAc/hexanes) to afford the title compound. LRMS (ESI) calc'd for $C_{24}H_{21}FN_6O_5$ $[M+H]^+$: 493, Found: 493.

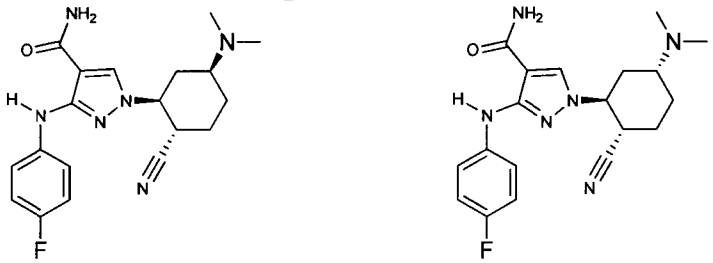
Step B: **1-[(1S,2S,4S and 1R,2R,4R)-2-Cyano-4-hydroxycyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide**

1-[(1S,3S,4S and 1R,3R,4R)-4-{4-carbamoyl-3-[(4-fluorophenyl)amino-1*H*-pyrazol-1-yl]-3-cyanocyclohexyl 2-nitrobenzoate (1.15 g, 2.34 mmol) was dissolved in THF (23.4 mL) and cooled to 0 °C. NaOMe (1.54 g, 12.5 mmol) was added after 5 minutes. The reaction was allowed to warm to ambient temperature for 45 minutes. The reaction mixture was partitioned between water and EtOAc, the layers were separated and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 50-100% EtOAc/hexanes followed by a gradient elution of 0-10% MeOH/DCM) to afford the title compound, **Example #5**. ^{1}HNMR (500 MHz, $CDCl_3$): δ 8.72 (s, 1H), 7.63 (s, 1H), 7.48-7.45 (m, 2H), 6.98 (t, J = 8.7 Hz, 2H), 5.40 (s, 2H), 4.0 (ddd, J = 11.5, 11.5, 4.5 Hz, 1H), 3.90-3.84 (m, 1H), 3.36-3.30 (m, 1H),

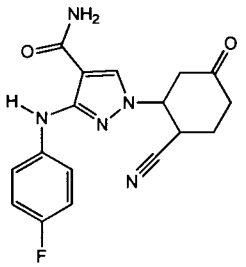
2.51 (qd, J = 3.5, 12.7 Hz, 1H), 2.29 (dq, J = 3.5, 14.0 Hz, 1H), 2.24-2.18 (m, 1H), 2.17-2.08 (m, 1H), 1.83-1.74 (m, 2H) 1.56-1.48 (m, 1H). LRMS (ESI) calc'd for $C_{17}H_{18}FN_5O_2$ $[M+H]^+$: 344, Found: 344.

Scheme #47

Example # 6-1 and 6-2



1-[(1S, 2S, 5S and 1R,2R,5R)-2-cyano-5-(dimethylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide and **1-[(1S, 2S, 5R and 1R,2R,5S)-2-cyano-5-(dimethylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide**



Step A: **1-(2-Cyano-5-oxocyclohexyl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide**

To a vial containing 1-(8-cyano-1,4-dioxaspiro[4.5]dec-7-yl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide (**Example #2-4**, 37 mg, 0.10 mmol) was added THF (0.38 mL), and 1N aqueous HCl (0.13 mL). The resulting mixture was heated to 75 °C for 5.5 hours. The reaction mixture was allowed to cool to ambient temperature and was diluted with EtOAc. The layers were separated and the organic layer was washed with water, saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in DMSO and purified by reverse-phase preparative HPLC (MeCN/water, with 0.1% v/v TFA modifier). Desired fractions were identified, combined, and lyophilized to afford the title compound as a 1:1 mixture of cis and trans isomers.

^{1}H NMR (600 MHz, DMSO-d_6) Cis isomer: δ 9.09 (br. S, 1H), 8.26 (s, 1H), 7.65 (br s, 1H), 7.53–7.45 (m, 2H), 7.24-7.12 (m, 3H), 6.83–6.76 (m, 1H), 5.07 (dd, J = 8.9, 5.2 Hz, 1H), 3.83 (dt, J = 9.9, 3.9 Hz, 1H), 3.08-2.01 (m, 6H). ^{1}H NMR (600 MHz, DMSO-d_6) Trans isomer: δ 9.17 (br. S, 1H), 8.21 (s, 1H), 7.65 (br s, 1H), 7.42–7.32 (m, 2H), 7.24-7.12 (m, 3H), 6.83–6.76 (m, 1H), 4.92 (td, J = 10.9, 4.8 Hz, 1H), 3.74 (td, J = 11.4, 3.5 Hz, 1H), 3.08-2.01 (m, 6H).

LRMS (ESI) calc'd for $C_{17}H_{17}N_5O_2$ $[M+H]^+$: 324, Found: 324.

Step B. **1-[(1S, 2S, 5S and 1R,2R,5R)-2-cyano-5-(dimethylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide and 1-[(1S, 2S, 5R and 1R,2R,5S)-2-cyano-5-(dimethylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide**

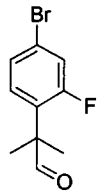
1-[(1S,2S and 1R,2R)-2-Cyano-5-oxocyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide was dissolved in MeOH (0.13 mL) and THF (0.13 mL). In a separate flask, dimethylamine (0.73 mL, 1.5 mmol, 2.0 M in THF) was dissolved in MeOH (0.13 mL) and THF (0.13 mL) before triethylamine (0.20 mL, 1.5 mmol) was added and the mixture was allowed to stir at ambient temperature for 2 minutes before it was added to the reaction vessel containing the dissolved ketone. Acetic acid (0.084 mL, 1.5 mmol) was added and stirring continued for 20 minutes before sodium cyanoborohydride (23 mg, 0.37 mmol) was added. The resulting reaction mixture was allowed to stir at ambient temperature for 18 hours before the reaction mixture was concentrated *in vacuo*. The residue was purified by reverse-phase preparative HPLC (using a gradient elution of MeCN/water, with 0.1% v/v TFA modifier). Desired fractions were identified, combined, and lyophilized to afford the title compounds:

Example #6-1: 1-[(1S, 2S, 5S and 1R,2R,5R)-2-cyano-5-(dimethylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide. ^{1}H NMR (600 MHz, acetone-d_6) δ 13.39 – 12.88 (m, 1H), 9.23 (s, 1H), 8.25 (s, 1H), 7.60 (dd, *J* = 8.2, 4.7, 2H), 7.20 (s, 1H), 6.98 (t, *J* = 8.5, 2H), 6.48 (s, 1H), 4.62 (td, *J* = 11.3, 3.4, 1H), 3.57 (t, *J* = 12.2, 1H), 3.49 (td, *J* = 11.8, 3.7, 1H), 3.03 (s, 6H), 2.63 (d, *J* = 10.5, 1H), 2.56 – 2.46 (m, 1H), 2.43 (dd, *J* = 24.3, 12.2, 1H), 2.34 (d, *J* = 12.4, 1H), 2.03 (s, 1H), 1.99 – 1.79 (m, 2H), 1.29 (dd, *J* = 14.3, 7.1, 1H). LRMS (ESI) calc'd for $C_{19}H_{23}F_3N_6O$ $[M+H]^+$: 371, Found: 371.

Example #6-2: 1-[(1S, 2S, 5R and 1R,2R,5S)-2-cyano-5-(dimethylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide. ^{1}H NMR (600 MHz, acetone-d_6) δ 12.29 (s, 1H), 9.17 (s, H), 8.61 (s, 1H), 7.57 (dd, *J* = 8.8, 4.6, 2H), 7.39 (s, 1H), 7.00 (t, *J* = 8.7, 2H), 6.45 (s, 1H), 4.96 (dd, *J* = 9.4, 4.8, 1H), 4.04 (d, *J* = 4.5, 1H), 3.87 (t, *J* = 9.4, 1H), 3.12 (s, 6H), 2.83 (d, *J* = 15.2, 1H), 2.65 – 2.51 (m, 1H), 2.29 – 2.14 (m, 2H), 2.11 (dd, *J* = 19.6, 9.7, 1H), 2.06 – 1.94 (m, 1H).

The following examples shown in **TABLE 14** were prepared according to **Scheme #47** following similar procedures described for **Examples #6-1** and **#6-2**, which can be achieved by those of ordinary skill in the art of organic synthesis.

reaction was quenched with saturated NH_4Cl aqueous solution (30 mL) at 0 °C. The solution was then extracted with EtOAc(3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by MPLC on Silica gel with 1-5 % EtOAc/hexane to afford 2-(4-bromo-2-fluorophenyl)-2-methylpropanenitrile as a yellow oil. MS ESI: $[M+H]^+$ *m/z* 242; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.23 (m, 3H), 1.75 (s, 6H).



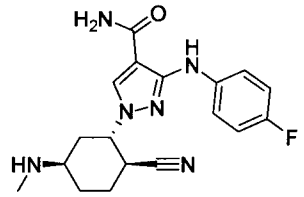
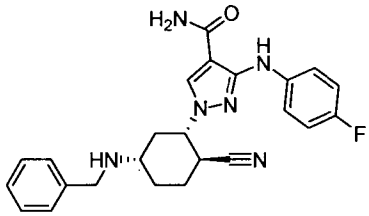
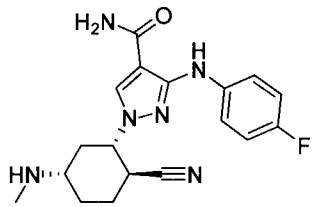
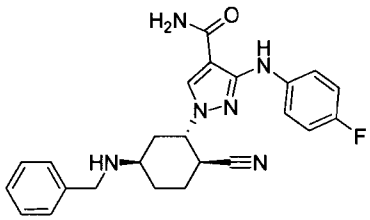
Step C: **2-(4-Bromo-2-fluorophenyl)-2-methylpropanal**

To a solution of 2-(4-bromo-2-fluorophenyl)-2-methylpropanenitrile (2.0 g, 8.3 mmol) in THF(20 mL) under nitrogen was added DIBAL-H (19 mL, 19 mmol, 1.0M in THF) dropwise at -30 °C. The resulting solution was stirred at ambient temperature for 3 hours before the addition of 2 N aqueous HCl (10 mL) at 0 °C. The mixture was stirred at ambient temperature for 10 minutes, then the solution was carefully basified with saturated aqueous $NaHCO_3$ to pH 8-9, and then extracted with EtOAc (3x50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by MPLC on Silica gel (eluting with 1-2 % EtOAc/hexane) to afford the title compound) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.32 – 7.21 (m, 1H), 7.18 – 7.03 (m, 2H), 1.41 (s, 6H). MS ESI: $[M+H]^+$ *m/z* 245.

Step D: ***(S* and *R)*-3-(4-bromo-2-fluorophenyl)-1,1,1-trifluoro-3-methylbutan-2-ol**

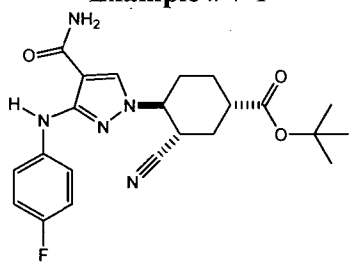
To a solution of 2-(4-bromo-2-fluorophenyl)-2-methylpropanal (2.4 g, 9.8 mmol) and trimethyl(trifluoromethyl)silane (2.8 g, 20 mmol) in THF(20 mL) under nitrogen was added a solution of TBAF (1.3 g, 4.8 mmol) in THF (5 mL) dropwise at -30 °C. The resulting solution was stirred at -30 °C for 1 hour and at ambient temperature for an additional 1 hour before 1 N aqueous HCl (10 mL) was added. The mixture was vigorously stirred at ambient temperature for 10 minutes, and then extracted with EtOAc (3x30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by MPLC on Silica gel (eluting with 1-3 % EtOAc/hexane) to the title compound as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.15 (m, 3H), 4.53 (q, J = 7.5 Hz, 1H), 2.30 (br, 1H), 1.41 (s, 6H). MS ESI: $[M+H]^+$ *m/z* 315.

TABLE 14:

Example	Structure	Compound Name	Exact Mass [M+H]+
6-3		1-{[(1S,2S,5R) and (1R,2R,5S)]-2-cyano-5-(methylamino)cyclohexyl}-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 357, found 357
6-4		1-{[(1S,2S,5S) and (1R,2R,5R)]-5-(benzylamino)-2-cyanocyclohexyl}-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 433, found 433
6-5		1-{[(1S,2S,5S) and (1R,2R,5R)-2-cyano-5-(methylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 357, found 357
6-6		1-{[(1S,2S,5R) and (1R,2R,5S)]-5-(benzylamino)-2-cyanocyclohexyl}-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 433, found 433

Scheme #30

Example # 7-1



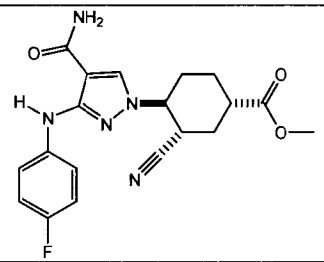
***tert*-Butyl (1S,3S,4S and 1R,3R,4R)-4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3- cyanocyclohexanecarboxylate**

3-[(4-Fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide (**Example #44-7**, 195 mg, 0.941 mmol) was added to a mixture of *tert*-butyl 3-cyanocyclohex-3-ene-1-carboxylate (249 mg, 1.13 mmol) in MeCN (4.7 mL). DBU (0.43 mL, 2.8 mmol) was added, the reaction vessel was capped and the reaction mixture was heated to 80 °C for 16 hours. The reaction mixture was cooled to ambient temperature, concentrated *in vacuo* and purified by reverse phase preparative

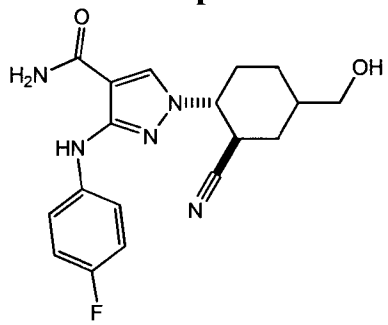
HPLC (using a gradient elution of 45-80% MeCN/water, with 0.1% v/v TFA modifier). Desired fractions were combined, basified with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The organic layer was dried over anhydrous $NaSO_4$, filtered, and concentrated *in vacuo* to afford the title compound, **Example # 7-1**. ^1H NMR (500 MHz, 10:1 $CDCl_3$:CD_3OD): δ 7.83 (s, 1H), 7.46-7.38 (m, 2H), 6.96-6.89 (m, 2H), 4.02-3.95 (m, 1H), 3.28-3.18 (m, 1H), 2.50-2.42 (m, 1H), 2.42-2.35 (m, 1H), 2.22-2.06 (m, 3H), 1.88-1.78 (m, 1H), 1.60-1.48 (m, 1H), 1.42 (s, 9H). LRMS (ESI) calc'd for $C_{22}H_{26}FN_5O_3$ $[M+H]^+$: 428, Found: 428.

The following examples shown in **TABLE 15** were prepared according to **Scheme #30** following similar procedures described for **Example #7-1**, which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 15:

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
7-2		methyl (1S,3S,4S and 1R,3R,4R)-4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3- cyanocyclohexanecarboxylate	Calc'd 386, Found 386

Example #8

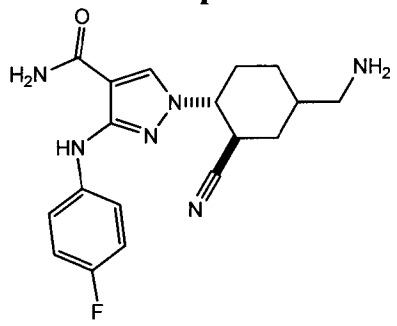


1-((1R,2R and 1S,2S)-2-Cyano-4-(hydroxymethyl)cyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide

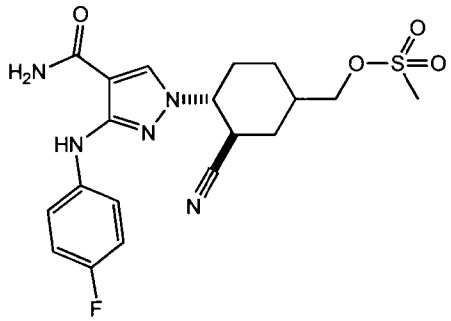
A solution of *tert*-butyl (1S,3S,4S and 1R,3R,4R)-4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3- cyanocyclohexanecarboxylate (**Example #7-1**, 50 mg, 0.12 mmol) in THF (1.1 mL) was stirred at ambient temperature and lithium borohydride (5 mg, 0.2 mmol) was added. The resulting mixture was stirred at 50 °C for 3 hours. The mixture was cooled to ambient temperature, diluted with water and extracted with EtOAc (2x). The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by MPLC on silica gel (using a

gradient elution of 0-5% MeOH/DCM). Desired fractions were identified, combined and concentrated *in vacuo* to afford the title compound. LRMS (ESI) calc'd for $C_{18}H_{20}FN_5O_2$ $[M+H]^+$: 358, Found: 358.

Example #9

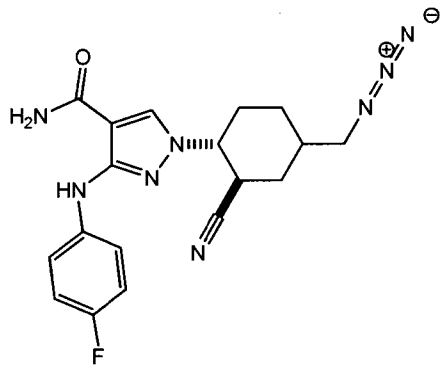


1-((1R,2R and 1S,2S)-4-(Aminomethyl)-2-cyanocyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide



Step A: ((3R,4R and 3S,4S)-4-(4-Carbamoyl-3-((4-fluorophenyl)amino)-1*H*-pyrazol-1-yl)-3-cyanocyclohexyl)methyl methanesulfonate

A solution of 1-((1R,2R and 1S,2S)-2-cyano-4-(hydroxymethyl)cyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide (**Example #8**, 50 mg, 0.14 mmol) in DCM (1.4 mL) was stirred at 0 °C. DIPEA (54 mg, 0.42 mmol) was added followed by the dropwise addition of methanesulfonyl chloride (19 mg, 0.17 mmol). The resulting mixture was stirred at 0 °C for 30 minutes then warmed to ambient temperature and stirred for an additional 1 hour. The mixture was carefully diluted with water and extracted with DCM (2x). The combined organic extracts were washed with 1N aqueous HCl, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by MPLC on silica gel (using a gradient elution of 0-5% MeOH/DCM). Desired fractions were identified, combined and concentrated *in vacuo* to afford the title compound. LRMS (ESI) calc'd for $C_{19}H_{22}FN_5O_4$ $[M+H]^+$: 436, Found: 436.



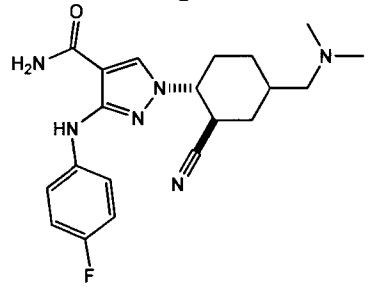
Step B: **1-((1R,2R and 1S,2S)-4-(Azidomethyl)-2-cyanocyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide**

To a solution of ((3R,4R and 3S,4S)-4-(4-carbamoyl-3-((4-fluorophenyl)amino)-1*H*-pyrazol-1-yl)-3-cyanocyclohexyl)methyl methanesulfonate (57 mg, 0.13 mmol) in DMF (1.3 mL) was added sodium azide (13 mg, 0.20 mmol). The resulting mixture was heated at 80 °C for 3 hours. The mixture was cooled to ambient temperature, diluted with water and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was carried on without further purification. LRMS (ESI) calc'd for $C_{18}H_{19}FN_8O$ $[M+H]^+$: 383, Found: 383.

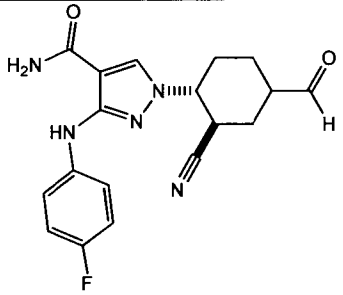
Step C: **1-((1R,2R and 1S,2S)-4-(aminomethyl)-2-cyanocyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide**

To a solution of 1-((1R,2R and 1S,2S)-4-(azidomethyl)-2-cyanocyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide (36 mg, 0.094 mmol) in THF (1 mL) was added resin bound triphenylphosphine (0.11 mmol). The resulting mixture was stirred at 0 °C for 30 mins before water (0.02 mL) was added. The resulting mixture was allowed to warm to ambient temperature and was stirred for 5 hours. The reaction mixture was filtered and the solids were flushed with DCM (2x). The filtrate was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by reverse-phase preparative HPLC (MeCN/water, with 0.1% v/v TFA modifier). Desired fractions were identified, combined, basified with saturated aqueous $NaHCO_3$, and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title compound. LRMS (ESI) calc'd for $C_{18}H_{21}FN_6O$ $[M+H]^+$: 357, Found: 357.

Example #10



1-((1R,2R and 1S,2S)-2-Cyano-4-((dimethylamino)methyl)cyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide



Step A: **1-((1R,2R and 1S,2S)-2-Cyano-4-formylcyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide**

1-((1R,2R and 1S,2S)-2-Cyano-4-(hydroxymethyl)cyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide (**Example #8**, 50 mg, 0.14 mmol) was dissolved in 1:1 DCM (0.7 mL):MeCN (0.7 mL). NMO (34 mg, 0.29 mmol) and 4Å molecular sieves (200 mg/mmol) were added and the reaction mixture was maintained at ambient temperature for 15 minutes. TPAP (10 mg, 0.03 mmol) was added to the reaction mixture and it was maintained at ambient temperature for 1 hour. The reaction mixture was then adsorbed on silica gel *in vacuo* and purified directly by MPLC on silica gel (using a gradient elution of 0-10%, MeOH/DCM). Desired fractions were identified, combined, and concentrated *in vacuo* to afford the title compound. LRMS (ESI) calc'd for $C_{18}H_{18}FN_5O_2$ $[M+H]^+$: 356, Found: 356.

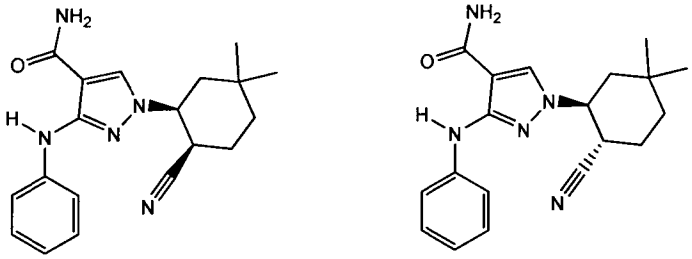
Step B: **1-((1R,2R and 1S,2S)-2-Cyano-4-((dimethylamino)methyl)cyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide**

To a solution of 1-((1R,2R and 1S,2S)-2-cyano-4-formylcyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide (24 mg, 0.068 mmol) in 1:1 MeOH:THF (1.3 mL) was added dimethylamine (0.034 mL, 0.68 mmol, 2M in THF), acetic acid (41 mg, 0.67 mmol) and sodium cyanoborohydride (11 mg, 0.17 mmol). The resulting mixture was maintained at ambient temperature for 1 hour. The crude reaction mixture was concentrated *in vacuo* and the resulting residue was purified by reverse phase preparative HPLC (using a gradient elution of 5-80% MeCN/water, with 0.1% v/v TFA modifier). Desired fractions were identified, combined, basified with saturated aqueous $NaHCO_3$, and extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and

concentrated *in vacuo* to afford the title compound. LRMS (ESI) calc'd for $C_{20}H_{25}FN_6O$ $[M+H]^+$: 385, Found: 385.

Scheme #30

Example #11-1 and 11-2



1-{[(1S,2S) and (1R,2R)]-2-Cyano-5,5-dimethylcyclohexyl}-3-(phenylamino)-1*H*-pyrazole-4-carboxamide *and* **1-{[(1S,2R) and (1R,2S)]-2-Cyano-5,5-dimethylcyclohexyl}-3-(phenylamino)-1*H*-pyrazole-4-carboxamide**

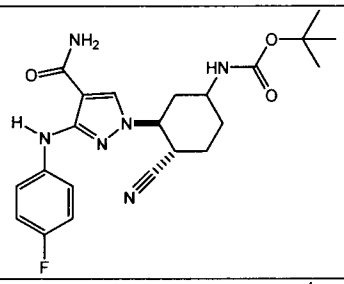
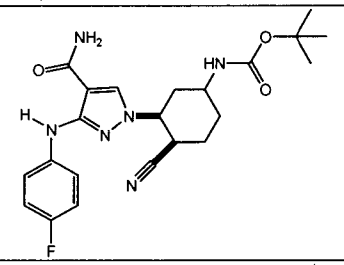
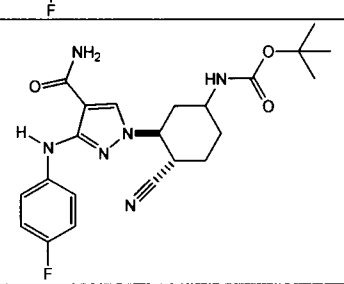
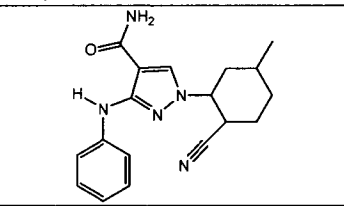
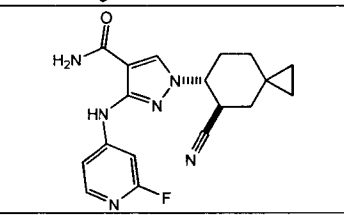
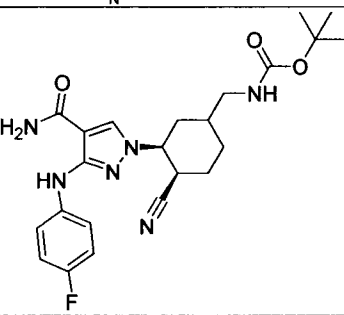
DBU (0.22 mL, 1.5 mmol) was added to a mixture of 3-(phenylamino)-1*H*-pyrazole-4-carboxamide (150 mg, 0.74 mmol) and 4,4-dimethylcyclohex-1-ene-1-carbonitrile (280 mg, 2.07 mmol) in ethanol (3.8 mL) and the vial capped and allowed to stir at 90 °C for 45 hours. The reaction mixture was concentrated *in vacuo* and the residue purified by MPLC on silica gel (using a gradient elution of 0-20% MeOH/DCM) to afford a 1:2 cis/trans mixture of the title compounds. This mixture was further purified by reverse-phase preparative HPLC (MeCN/water, with 0.1% v/v TFA modifier) to afford the title compounds.

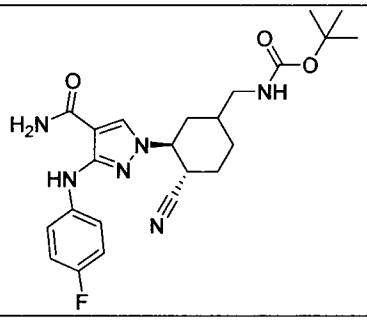
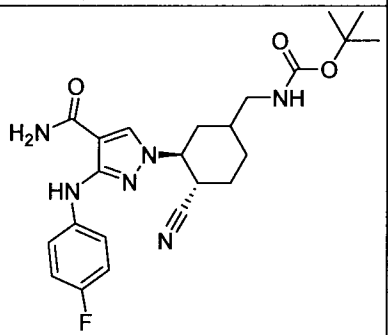
Example #11-1: ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.08 (s, 1H), 8.32 (s, 1H), 7.55 (s, 1H), 7.50 (d, 2H), 7.20 (dd, J = 8.5, 7.4, 2H), 7.08 (s, 1H), 6.79 (t, J = 7.3, 1H), 4.47 (m, 1H), 3.78 – 3.73 (m, 1H), 2.06 – 1.95 (m, 1H), 1.85 (dd, J = 14.2, 2.5, 2H), 1.76 (t, J = 12.8, 1H), 1.44 – 1.32 (m, J = 14.2, 10.5, 2H), 1.02 (d, J = 32.8, 6H). LRMS (ESI) calc'd for $C_{19}H_{23}N_5O$ $[M+H]^+$: 338, Found: 338.

Example #11-2: ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.20 (s, 1H), 7.60 (s, 1H), 7.46 (d, J = 7.8, 2H), 7.22 (t, J = 7.9, 2H), 7.10 (s, 1H), 6.79 (t, J = 7.3, 1H), 4.50 (td, J = 11.9, 4.2, 1H), 3.20 – 3.10 (m, 1H), 2.02 (dd, J = 13.4, 3.3, 1H), 1.87 (ddd, J = 26.5, 13.2, 3.6, 1H), 1.71 (t, J = 12.7, 1H), 1.64 (d, J = 10.1, 1H), 1.38 (d, J = 13.6, 1H), 1.35 – 1.23 (m, 1H), 0.96 (d, J = 36.2, 6 H). LRMS (ESI) calc'd for $C_{19}H_{23}N_5O$ $[M+H]^+$: 338, Found: 338.

The following examples shown in **TABLE 16** were prepared according to **Scheme #30** following similar procedures described for **Example #11-1**, which can be achieved by those of ordinary skill in the art of organic synthesis.

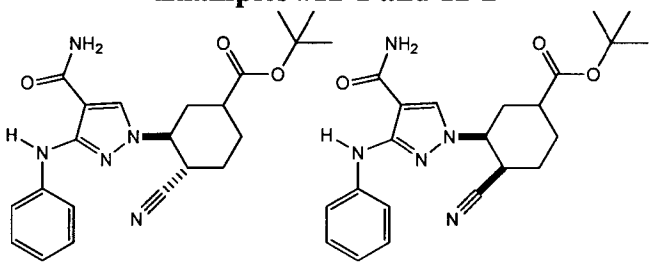
TABLE 16:

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
11-3		*tert*-butyl [(1R,3S,4S and 1S,3R,4R) or (1S,3S,4S and 1R,3R,4R)-3-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-4-cyanocyclohexyl]carbamate	Calc'd 443, Found 443
11-4		*tert*-butyl [(3R,4S and 3S,4R)-3-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-4-cyanocyclohexyl]carbamate	Calc'd 443, Found 443
11-5		*tert*-butyl [(1R,3S,4S and 1S,3R,4R) or (1S,3S,4S and 1R,3R,4R)-3-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-4-cyanocyclohexyl]carbamate	Calc'd 443, Found 443
11-6		1-(2-cyano-5-methylcyclohexyl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 324, Found 324
11-7		1-((5R,6R and 5S,6S)-5-cyanospiro[2.5]octan-6-yl)-3-((2-fluoropyridin-4-yl)amino)-1*H*-pyrazole-4-carboxamide	Calc'd 355, Found 355
11-8		tert-butyl {[(3S,4R) and (3R,4S)]-3-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-4-cyanocyclohexyl]methyl}carbamate	Calc'd 457, found 457

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
11-9		tert-butyl {[(1R or S 3S,4S) and (1S or R, 3R, 4R)] -3-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-4-cyanocyclohexyl]methyl}carbamate	Calc'd 457, found 457
11-10		tert-butyl {[(1S or R,3S,4S) and (1R or S,3R, 4R)] -3-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-4-cyanocyclohexyl]methyl}carbamate	Calc'd 457, found 457

Scheme #30

Examples #12-1 and 12-2



(3S,4S and 3R,4R)-tert-butyl 3-(4-carbamoyl-3-(phenylamino)-1H-pyrazol-1-yl)-4-cyanocyclohexanecarboxylate *and* **(3S,4R and 3R,4S)-tert-butyl 3-(4-carbamoyl-3-(phenylamino)-1H-pyrazol-1-yl)-4-cyanocyclohexanecarboxylate**

3-(Phenylamino)-1*H*-pyrazole-4-carboxamide (**Example #44-1**, 50 mg, 0.25 mmol) was combined with DBU (75 mg, 0.50 mmol) and *tert*-butyl 4-cyanocyclohex-3-ene-1-carboxylate (100 mg, 0.50 mmol) in *t*-BuOH (1.2 mL). The reaction mixture was heated to 90 °C and allowed to stir for 18 hours. The mixture was then cooled to 23 °C and purified directly by reverse-phase preparative HPLC (MeCN/water, with 0.1% v/v TFA modifier). Desired fractions were identified, combined, and concentrated *in vacuo* to afford the title compounds.

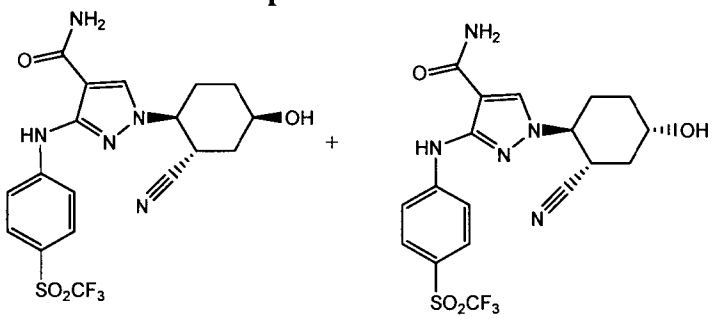
Example # 12-1: (3S,4S and 3R,4R)-tert-butyl 3-(4-carbamoyl-3-(phenylamino)-1H-pyrazol-1-yl)-4-cyanocyclohexanecarboxylate: ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.67 (s, 1H), 7.61 (s, 1H),

7.51 (d, J = 8.0 Hz, 2H), 7.26 (t, J = 7.9 Hz, 2H), 6.87 (t, J = 7.2 Hz, 1H), 5.56 (br. S, 2H), 4.46 (td, J = 11.7, 3.9 Hz, 1H), 3.22 (br. S, 1H), 3.07–2.96 (m, 1H), 2.41 (td, J = 13.2, 4.5 Hz, 1H), 2.26 (d, J = 14.0 Hz, 1H), 2.22–2.13 (m, 1H), 2.10 (d, J = 13.6 Hz, 1H), 1.98–1.89 (m, 1H), 1.79-1.71 (m, 1H), 1.26 (s, 9H). LRMS (ESI) calc'd for $C_{22}H_{27}N_5O_3$ $[M+H]^+$ 410, Found 410.

Example #12-2: (3S,4R and 3R,4S)-tert-butyl 3-(4-carbamoyl-3-(phenylamino)-1H-pyrazol-1-yl)-4-cyanocyclohexanecarboxylate. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.72 (s, 1H), 7.72 (s, 1H), 7.51 (d, J = 7.8 Hz, 2H), 7.26 (t, J = 7.9 Hz, 2H), 6.88 (t, J = 7.3 Hz, 1H), 5.55 (s, 2H), 4.31 (dt, J = 12.9, 3.5 Hz, 1H), 3.73–3.68 (m, 1H), 2.49–1.49 (m, 7H), 1.23 (s, 9H). LRMS (ESI) calc'd for $C_{22}H_{27}N_5O_3$ $[M+H]^+$ 410, Found 410.

Scheme #31

Examples #13-1 and 13-2



1-[(1S,2S,4R and 1R,2R,4S)-2-Cyano-4-hydroxycyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide and **1-[(1S,2S,4S and 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide**

Nitrogen was bubbled through a mixture of 3-amino-1-[(1S,2S and 1R,2R)-2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide (**Intermediates #48-1 and 48-2**, 2.00 g, 8.02 mmol), 1-bromo-4-[(trifluoromethyl)sulfonyl]benzene (2.32 g, 8.02 mmol), K_3PO_4 (2.38 g, 11.2 mmol), and X-Phos (1.15 g, 2.41 mmol) in dioxane (27 mL) for 5 minutes, and then $Pd_2(dba)_3$ (735 mg, 0.802 mmol) was added. The reaction vessel was sealed, and heated to 105 °C. After 40 minutes, the reaction mixture was cooled to ambient temperature and partitioned between EtOAc and water. The organic layer was washed with saturated aqueous sodium chloride solution, and the washed solution was filtered. The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel (using a gradient elution of 60-100%, EtOAc/hexanes followed by a gradient elution of 5%-10%, MeOH/DCM) to afford the title compounds.

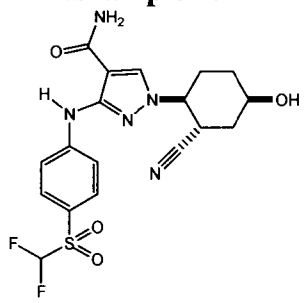
Example 13-1: 1-[(1S,2S,4R and 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide. ^{1}HNMR (500 MHz, CD_3OD): δ 8.22 (s, 1H), 7.92-7.87 (m, 4H), 4.38 (td, J = 11.5, 4.0 Hz, 1H), 4.15-4.12 (m, 1H),

3.69 (td, J = 11.7, 3.7 Hz, 1H), 2.46 (qd, 13.5, 3.6 Hz, 1H), 2.31-2.26 (m, 1H), 2.05-1.88 (m, 3H), 1.80-1.73 (m, 1H). LRMS (ESI) calc'd for $C_{18}H_{19}F_3N_5O_4S$ $[M+H]^+$: 458, Found: 458.

Example 13-2: 1-[(1S,2S,4S and 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide. ^{1}HNMR (500 MHz, CD_3OD): δ 8.19 (s, 1H), 7.92-7.85 (m, 4H), 4.38 (td, 11.0, 4.0 Hz, 1H), 3.81-3.74 (m, 1H), 3.56-3.49 (m, 1H), 2.46-2.40 (m, 1H), 2.23-2.06 (m, 3H), 1.76 (q, J = 12.1 Hz, 1H), 1.58-1.49 (m, 1H). LRMS (ESI) calc'd for $C_{18}H_{19}F_3N_5O_4S$ $[M+H]^+$: 458, Found: 458.

Scheme #31

Example #14

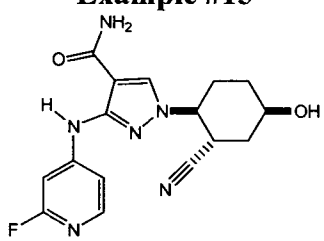


1-[(1S,2S,4R and 1R,2R,4S)-2-Cyano-4-hydroxycyclohexyl]-3-({4-[(difluoromethyl) sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide

Nitrogen was bubbled through a mixture of 3-amino-1-[(1S,2S,4R and 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide (**Intermediate #48-1**, 200 mg, 0.802 mmol), 1-bromo-4-[(difluoromethyl)sulfonyl]benzene (217 mg, 0.802 mmol), K_3PO_4 (0.238 g, 1.12 mmol), and X-Phos (115 mg, 0.241 mmol) in dioxane (2.7 mL) for 5 minutes, and then $Pd_2(dba)_3$ (73 mg, 0.080 mmol) was added. The reaction vessel was sealed, and heated to 105 °C. After 60 minutes, the reaction mixture was cooled to 23 °C and partitioned between EtOAc and water. The organic layer was washed with saturated aqueous sodium chloride solution, and the washed solution was filtered. The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel (using a gradient elution of 60-100%, EtOAc/hexanes) to afford the title compound. **Example # 14.** ^{1}HNMR (500 MHz, CD_3OD): δ 8.20 (s, 1H), 7.85-7.80 (m, 4H), 6.62 (t, JH-$_F$ = 53.4 Hz, 1H), 4.35 (td, J = 11.5, 4.0 Hz, 1H), 4.14-4.10 (m, 1H), 3.72-3.66 (m, 1H), 2.47 (qd, J = 13.4, 3.4 Hz, 1H), 2.29-2.24 (m, 1H), 2.04-1.86 (m, 3H), 1.74 (tt, J = 13.5, 2.9 Hz, 1H). LRMS (ESI) calc'd for $C_{18}H_{20}F_2N_5O_4S$ $[M+H]^+$: 440, Found: 440.

Scheme #31

Example #15

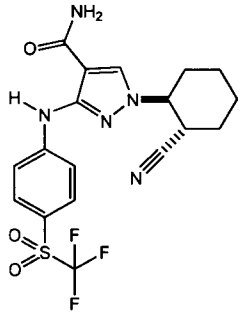


1-[(1S,2S,4R and 1R,2R,4S)-2-Cyano-4-hydroxycyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide

Nitrogen was bubbled through a mixture of 3-amino-1-[(1S,2S,4R and 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide (**Intermediate #48-1**, 200 mg, 0.802 mmol), 4-bromo-2-fluoropyridine (141 mg, 0.802 mmol), K_3PO_4 (0.238 g, 1.12 mmol), and X-Phos (115 mg, 0.241 mmol) in dioxane (2.7 mL) for 5 minutes, and then $Pd_2(dba)_3$ (73 mg, 0.080 mmol) was added. The reaction vessel was sealed, and heated to 105 °C. After 40 minutes, the reaction mixture was cooled to 23 °C and partitioned between EtOAc and water. The organic layer was washed with saturated aqueous sodium chloride solution, and the washed solution was filtered. The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel (using a gradient elution of 60-100% EtOAc/hexanes) to afford the title compound, **Example # 15**. ^{1}HNMR (500 MHz, CD_3OD): δ 8.20 (s, 1H), 7.89 (d, J = 5.4 Hz, 1H), 7.43 (s, 1H), 7.23 (d, J = 6.0 Hz, 1H), 4.37 (td, J = 11.5, 3.8 Hz, 1H), 4.14-4.11 (m, 1H), 3.70-3.54 (m, 1H), 2.47 (qd, J = 13.2, 3.7 Hz, 1H), 2.30-2.26 (m, 1H), 2.04-1.87 (m, 3H), 1.79-1.73 (m, 1H). LRMS (ESI) calc'd for $C_{16}H_{18}N_6O_4$ $[M+H]^+$: 345, Found: 345.

Scheme #31

Example #16



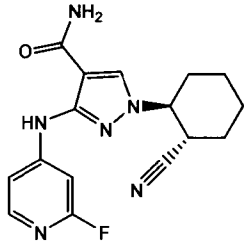
1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide

Nitrogen was bubbled through a mixture of 3-amino-1-[(1*S*,2*S* and 1*R*,2*R*)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide (**Intermediate #48-3**, 20.2 g, 87.0 mmol), 1-bromo-4-[(trifluoromethyl)sulfonyl]benzene (27.5 g, 95.0 mmol), K_3PO_4 (27.6 g, 130 mmol), X-Phos (4.54 g, 9.53 mmol), and $Pd_2(dba)_3$ (3.96 g, 4.33 mmol) in dioxane (202 mL). The reaction mixture was then heated to 80 °C. After 3 hours, the reaction mixture was cooled to ambient temperature, diluted with ethyl acetate, and filtered through celite. The crude filtrate was adsorbed onto silica gel, and purified by MPLC on silica gel (eluting with MeOH/DCM). Desired fractions were identified, combined and concentrated *in vacuo*. The residue was dissolved in ethyl acetate, hexane was then added to the solution, which resulted in recrystallization. The slurry was stirred for 30 minutes, and was then filtered to afford the title compound, **Example #16**. ^{1}HNMR (600 MHz, $CDCl_3$): δ 9.58 (s, 1H), 7.91 (d, J = 9.0 Hz, 2H), 7.30 (d, J = 9.0 Hz, 2H), 7.73 (s, 1H), 5.59 (s, 2H), 4.06-4.00 (m, 1H), 3.19-3.13 (m, 1H), 2.35

(br d, J = 12.0 Hz, 1H), 2.16-2.12 (m, 2H), 2.01 (br d, J = 13.2 Hz, 1H), 1.91 (br d, J = 11.7 Hz, 1H), 1.78-70 (m, 1H), 1.49-40 (m, 2H). LRMS (ESI) calc'd for $C_{18}H_{19}F_3N_5O_3S$ $[M+H]^+$: 442, Found: 442.

Scheme #31

Example #17-1

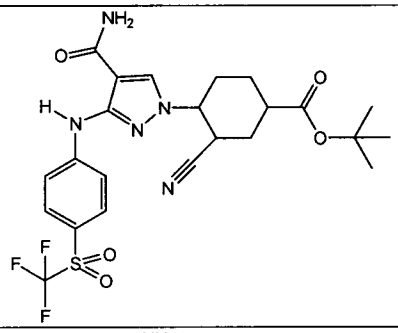
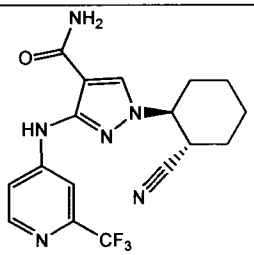
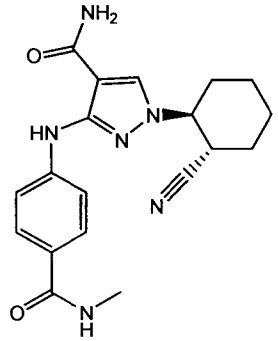
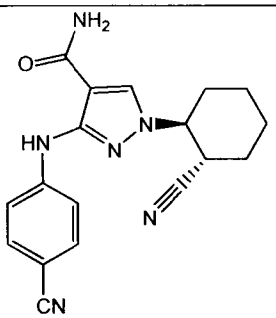


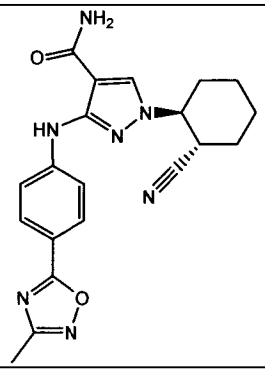
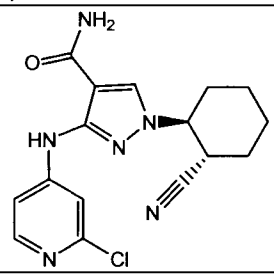
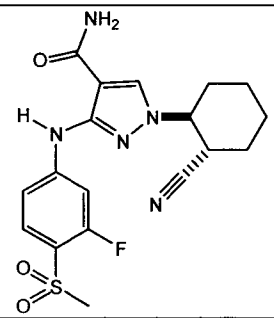
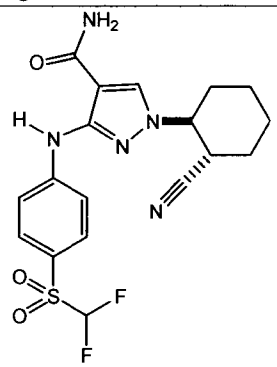
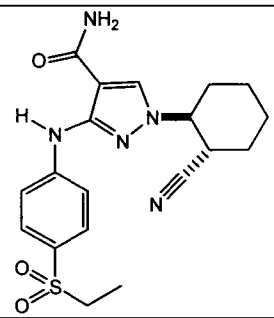
1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide

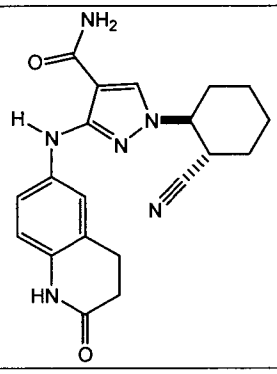
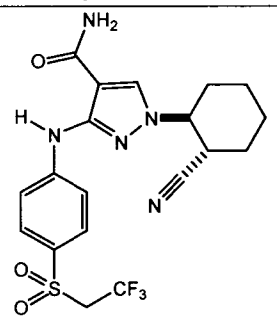
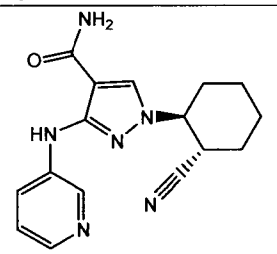
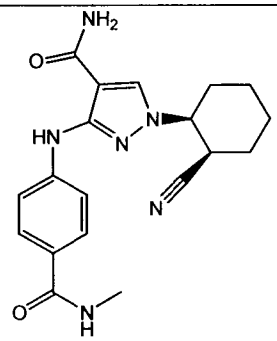
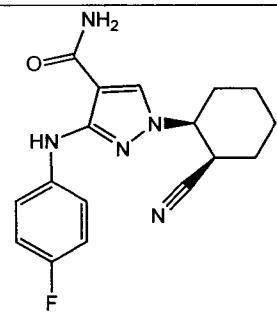
Nitrogen was bubbled through a mixture of 3-amino-1-[(1*S*,2*S* and 1*R*,2*R*)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide (**Intermediate #48-3**, 4.82 g, 20.7 mmol), 4-bromo-2-fluoropyridine (5.45 g, 31.0 mmol), K_3PO_4 (6.58 g, 31.0 mmol), and X-Phos (2.96 g, 6.20 mmol) in dioxane (67 mL) for 5 minutes, and then $Pd_2(dba)_3$ (1.89 g, 2.07 mmol) was added. The reaction vessel was sealed, and heated to 100 °C. After 4 hours, the reaction mixture was cooled to ambient temperature, and additional portions of X-Phos (500 mg, 1.00 mmol) and $Pd_2(dba)_3$ (500 mg, 0.540 mmol) were added. The reaction vessel was sealed and heated to 100 °C for an additional 45 minutes, and was then cooled to ambient temperature. The cooled reaction mixture was partitioned between EtOAc and water. The organic layer was washed with saturated aqueous sodium chloride solution, and the washed solution was filtered. The filtrate was concentrated and the residue was purified by MPLC on silica gel (using a gradient elution of 85-100% EtOAc/hexanes) to afford the title compound, **Example #17-1**. ^{1}HNMR (500 MHz, CD_3OD): δ 8.18 (s, 1H), 7.90 (d, J = 6.0 Hz, 1H), 7.41 (d, J = 1.0 Hz, 1H), 7.23 (d, J = 5.5 Hz, 1H), 4.31 (td, J = 11.5, 3.8 Hz, 1H), 3.32-3.27 (m, 1H), 2.32-2.27 (m, 1H), 2.14-2.08 (m, 1H), 2.02 (qd, J = 12.2, 3.7 Hz, 1H), 1.97-1.92 (m, 1H), 1.88-1.74 (m, 2H), 1.59-1.40 (m, 2H). LRMS (ESI) calc'd for $C_{16}H_{18}FN_6O$ $[M+H]^+$: 329, Found: 329.

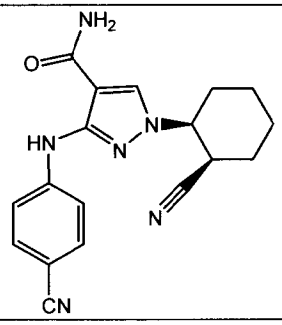
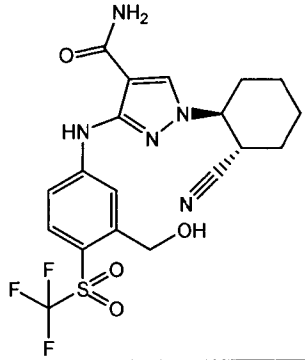
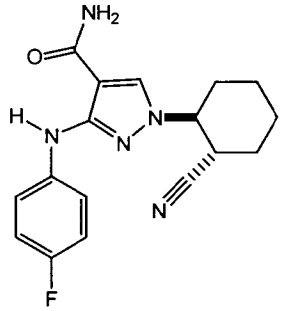
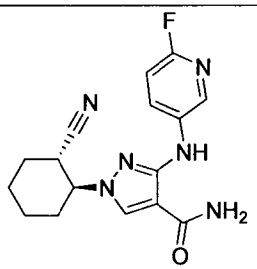
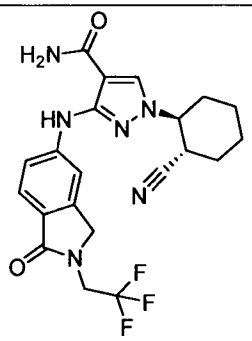
The following examples, disclosed in **TABLE 17** were prepared according to **Scheme #31** following similar procedures described for **Example #17-1**, and optionally using the chiral resolution methods described for **Examples 42-45** or the chiral **Intermediates 50-1** and **50-2** which can be achieved by those of ordinary skill in the art of organic synthesis.

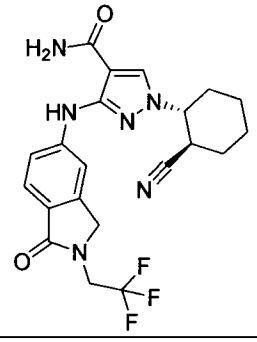
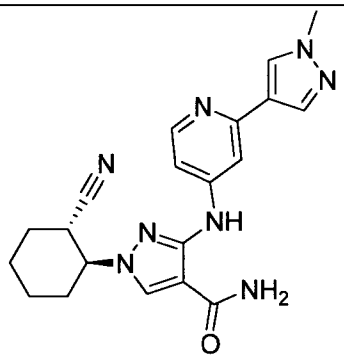
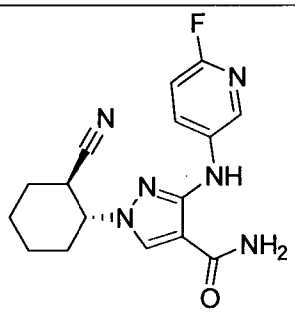
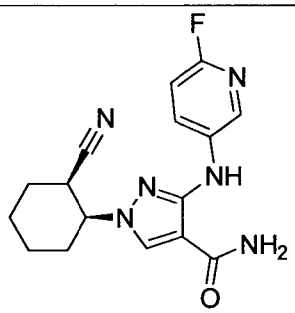
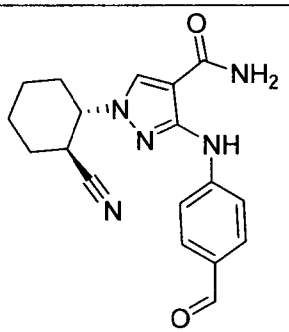
TABLE 17:

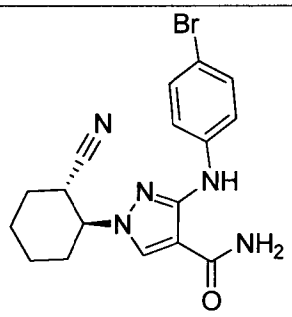
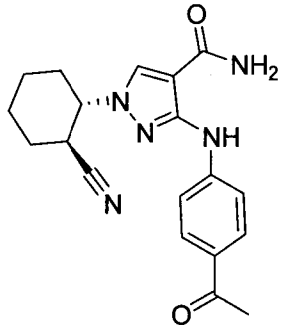
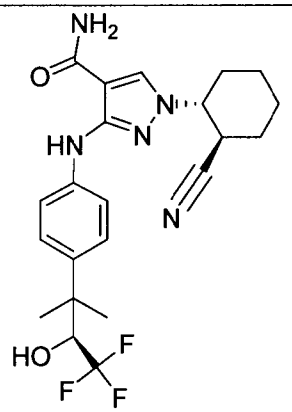
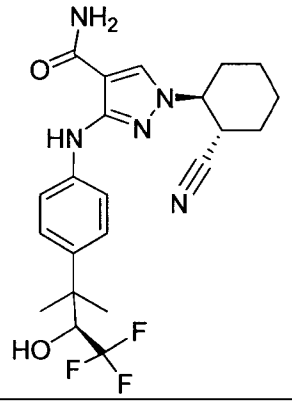
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-2		*tert*-butyl 4-[4-carbamoyl-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazol-1-yl]-3-cyanocyclohexanecarboxylate	Calc'd 542, Found 542
17-3		1-[(1S,2S and 1R,2R)-2-Cyanocyclohexyl]-3-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 379, Found 379
17-4		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-{[4-(methylcarbamoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 367, Found 367
17-5		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-[(4-cyanophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 335, Found 335

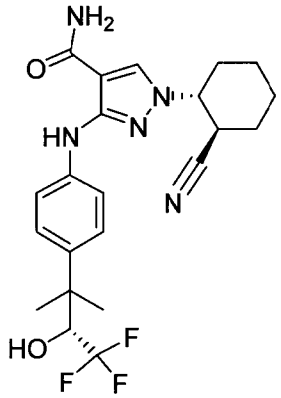
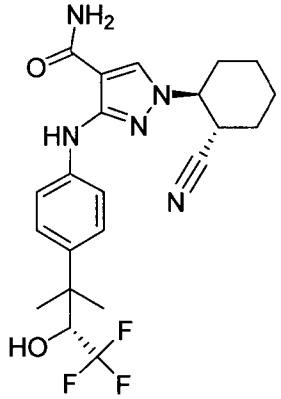
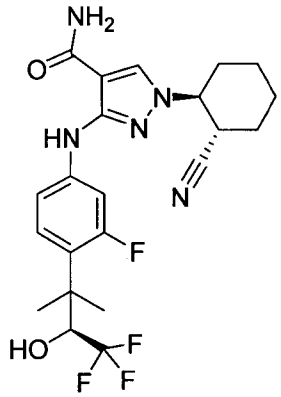
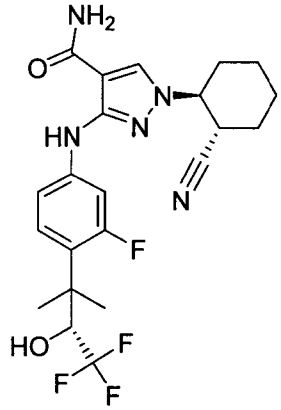
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-6		1-[(1S,2S and 1R,2S)-2-cyanocyclohexyl]-3-{[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl] amino}-1*H*-pyrazole-4-carboxamide	Calc'd 392, Found 392
17-7		3-[(2-chloropyridin-4-yl)amino]-1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 345, Found 345
17-8		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-{[3-fluoro-4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 406, Found 406
17-9		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-({4-[(difluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 424, Found 424
17-10		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-{[4-(ethylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 402, Found 402

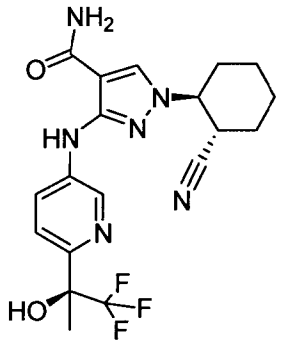
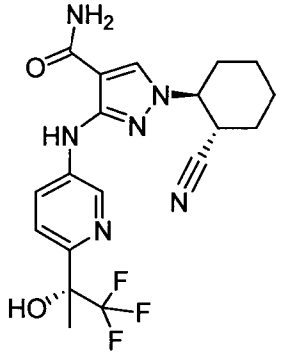
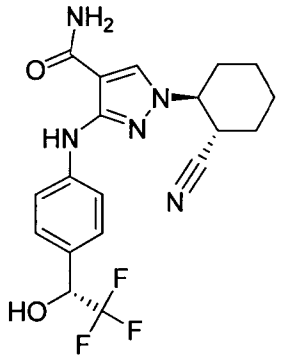
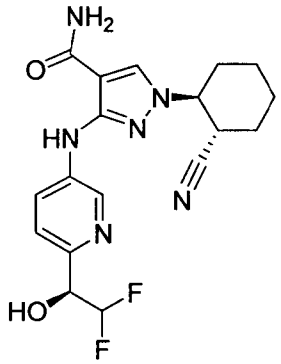
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-11		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-[(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 379, Found 379
17-12		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-({4-[(2,2,2-trifluoroethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 456, Found 456
17-13		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-(pyridin-3-ylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 311, Found 311
17-14		1-[(1S,2R and 1R,2S)-2-cyanocyclohexyl]-3-{[4-(methylcarbamoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 367, Found 367
17-15		1-[(1S,2R and 1R,2S)-2-cyanocyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 328, Found 328

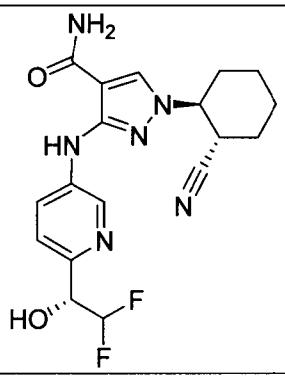
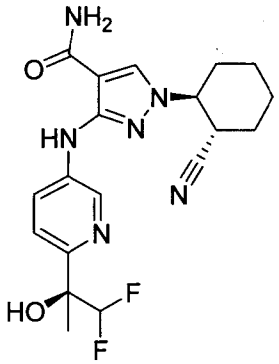
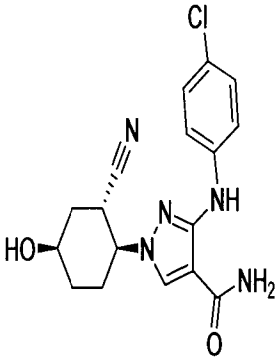
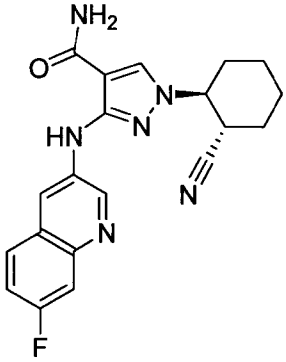
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-16		1-[(1S,2R and 1R,2S)-2-cyanocyclohexyl]-3-[(4-cyanophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 335, Found 335
17-17		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-({3-(hydroxymethyl)-4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 472, Found 472
17-18		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 328, Found 328
17-19		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-[(6-fluoropyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 329, found 329
17-20		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-{[1-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-isoindol-5-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 447, found 447

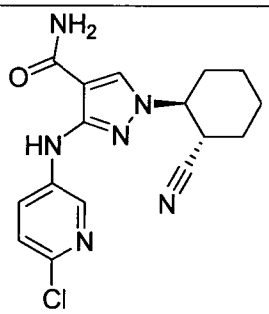
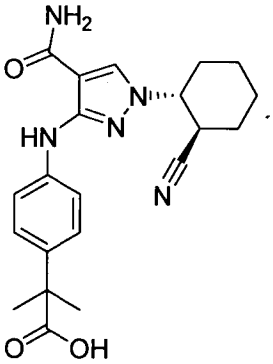
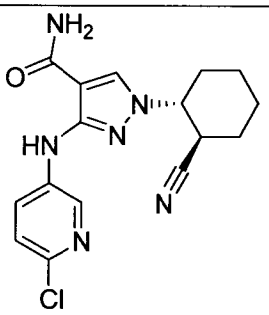
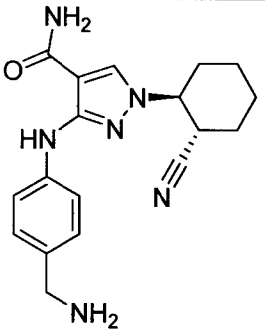
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-21		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-{[1-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-isoindol-5-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 447, found 447
17-22		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-{[2-(1-methyl-1*H*-pyrazol-4-yl)pyridin-4-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 391, found 391
17-23		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-[(6-fluoropyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 329., found 329
17-24		1-[(1S,2R and 1R,2S)-2-cyanocyclohexyl]-3-[(6-fluoropyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 329, found 329
17-25		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-[(4-formylphenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 338, found 338

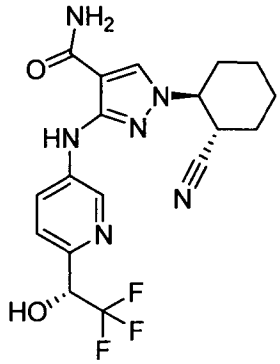
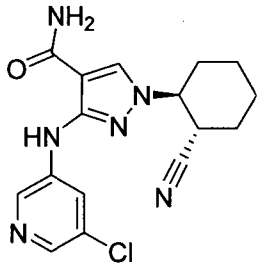
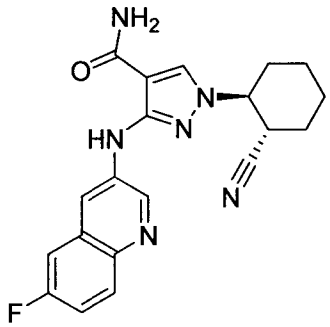
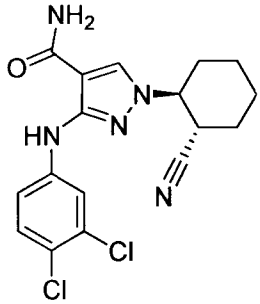
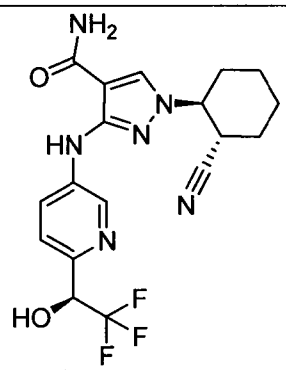
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-26		3-[(4-bromophenyl)amino]-1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 388, found 388
17-27		3-[(4-acetylphenyl)amino]-1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 352, found 352
17-28		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-({4-[(2S or 2R)-3,3,3-trifluoro-2-hydroxy-1,1-dimethylpropyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 450, found 450
17-29		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-({4-[(2S or 2R)-3,3,3-trifluoro-2-hydroxy-1,1-dimethylpropyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 450, found 450

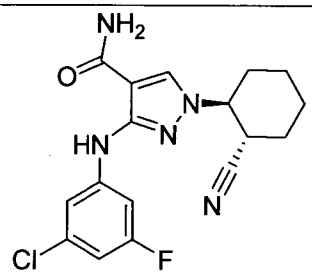
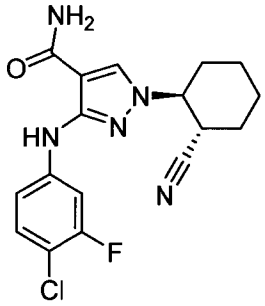
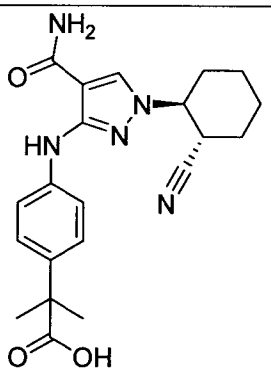
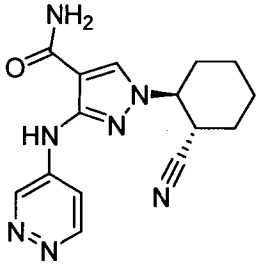
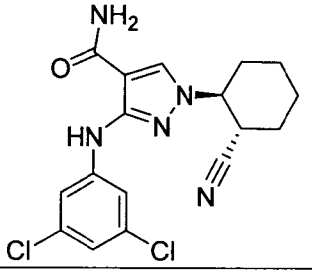
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-30		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-({4-[(2R or 2S)-3,3,3-trifluoro-2-hydroxy-1,1-dimethylpropyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 450, found 450
17-31		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-({4-[(2R or 2S)-3,3,3-trifluoro-2-hydroxy-1,1-dimethylpropyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 450, found 450
17-32		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-({3-fluoro-4-[(2S or 2R)-3,3,3-trifluoro-2-hydroxy-1,1-dimethylpropyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 468, found 468
17-33		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-({3-fluoro-4-[(2R or 2S)-3,3,3-trifluoro-2-hydroxy-1,1-dimethylpropyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 468, found 468

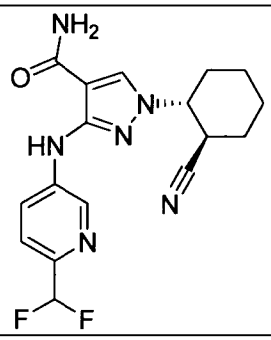
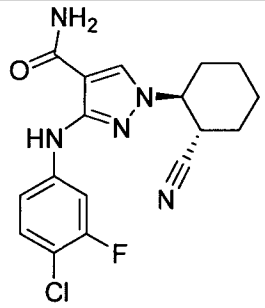
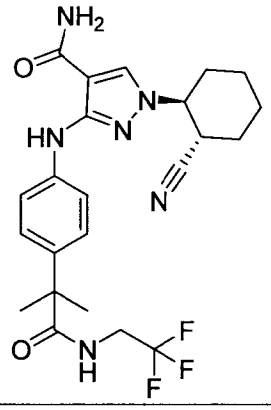
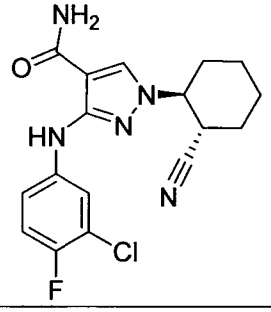
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-34		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-({6-[(1S or 1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 423, found 423
17-35		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-({6-[(1R or 1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 423, found 423
17-36		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 408, found 498
17-37		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-({6-[(1S or 1R)-2,2-difluoro-1-hydroxyethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 391, found 391

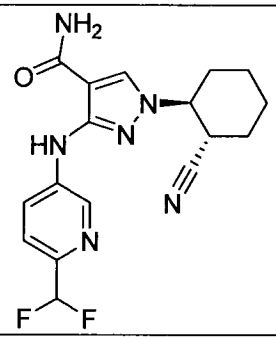
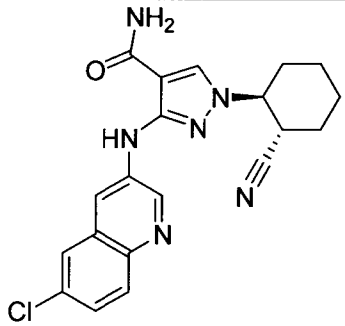
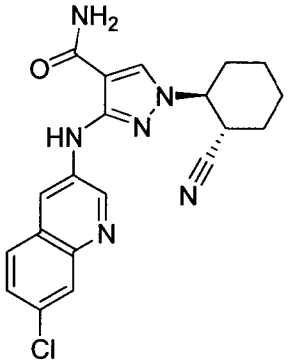
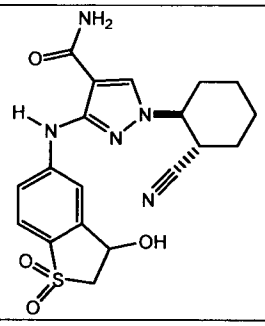
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-38		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-({6-[(1R or 1S)-2,2-difluoro-1-hydroxyethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 391, found 391
17-39		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-({6-[(1S or 1R)-2,2-difluoro-1-hydroxy-1-methylethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 405, found 405
17-40		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-({6-[(1R or 1S)-2,2-difluoro-1-hydroxy-1-methylethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 405, found 405
17-41		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-[(7-fluoroquinolin-3-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 379.0, found 379

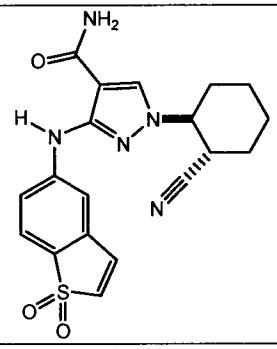
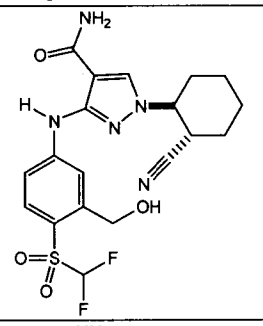
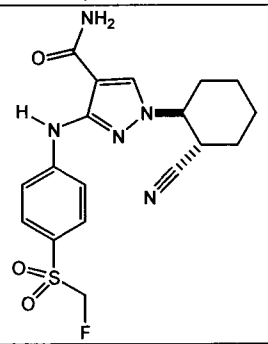
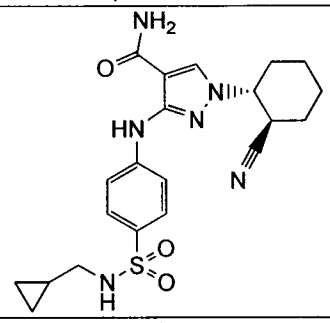
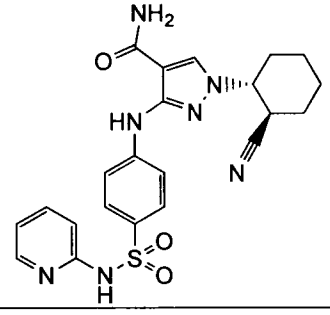
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-42		3-[(6-chloropyridin-3-yl)amino]-1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 345, found 345
17-43		2-[4-({4-carbamoyl-1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]-2-methylpropanoic acid	Calc'd 396, found 396
17-44		3-[(6-chloropyridin-3-yl)amino]-1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 345, found 345
17-45		3-{[4-(aminomethyl)phenyl]amino}-1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 339, found [M-NH_2]322

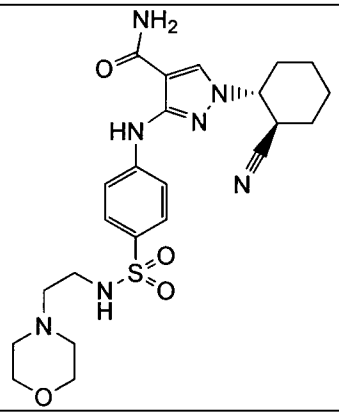
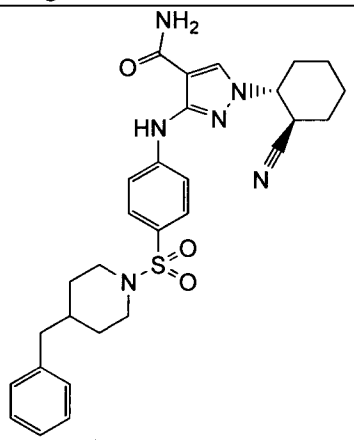
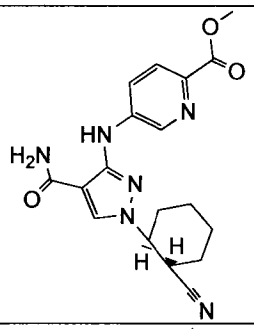
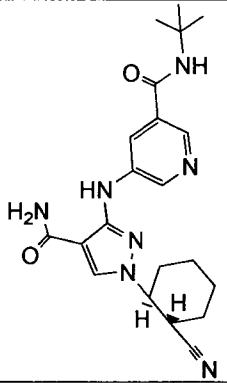
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-46		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-({6-[(1R or 1S)-2,2,2-trifluoro-1-hydroxyethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 409, found 409
17-47		3-[(5-chloropyridin-3-yl)amino]-1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 345, found 345
17-48		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-[(6-fluoroquinolin-3-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 379, found 379
17-49		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-[(3,4-dichlorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 378, found 378
17-50		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-({6-[(1S or 1R)-2,2,2-trifluoro-1-hydroxyethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 409, found 409

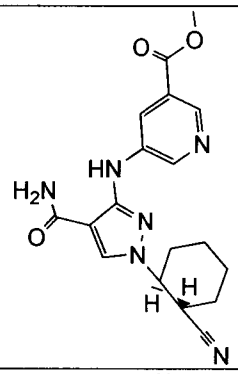
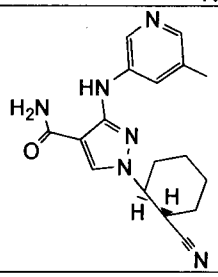
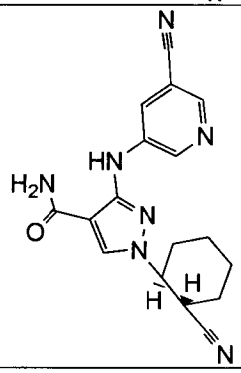
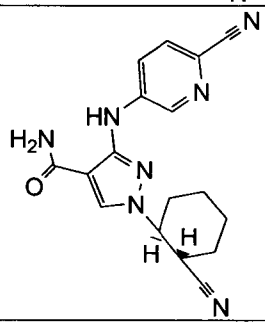
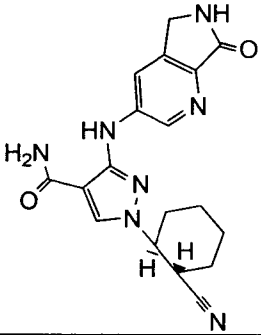
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-51		3-[(3-chloro-5-fluorophenyl)amino]-1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 362, found 362
17-52		3-[(4-chloro-3-fluorophenyl)amino]-1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 362, found 362
17-52		2-[4-({4-carbamoyl-1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]-2-methylpropanoic acid	Calc'd 396, found 396
17-53		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-(pyridazin-4-ylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 312, found 312
17-54		1-[(1S,2S or 1R, 2R)-2-cyanocyclohexyl]-3-[(3,5-dichlorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 378, found 378

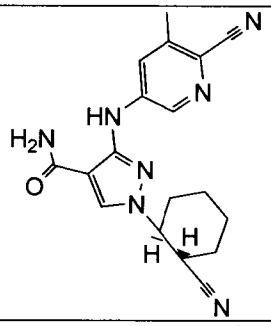
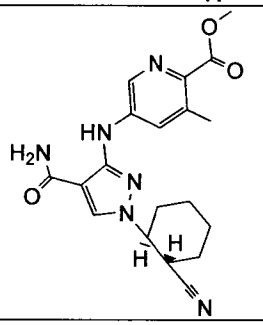
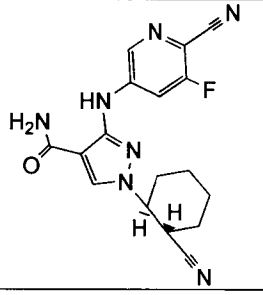
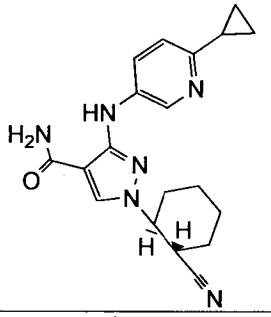
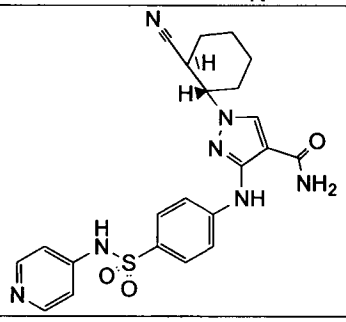
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-55		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-{[6-(difluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 361, found 361
17-56		3-[(4-chloro-3-fluorophenyl)amino]-1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 362, found 362
17-57		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-[(4-{1,1-dimethyl-2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl}phenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 477, found 477
17-58		3-[(3-chloro-4-fluorophenyl)amino]-1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 362, found 362

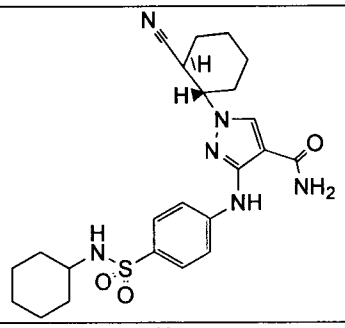
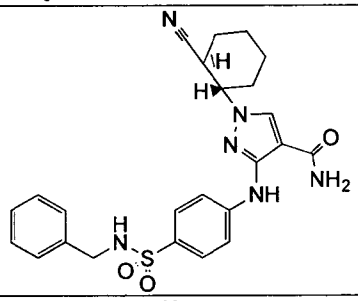
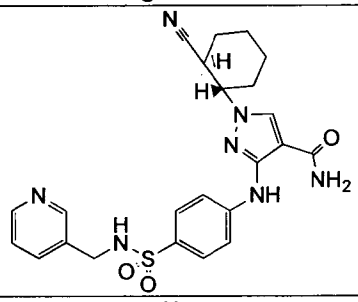
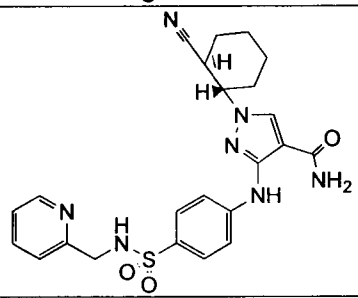
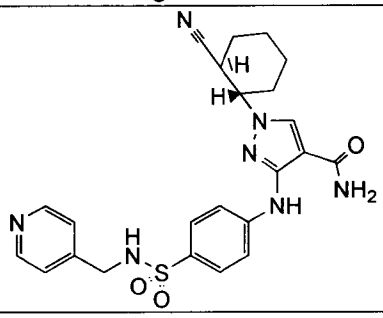
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-59		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-{[6-(difluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 361, found 361
17-60		3-[(6-chloroquinolin-3-yl)amino]-1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 395, found 395
17-61		3-[(7-chloroquinolin-3-yl)amino]-1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 395, found 395
17-62		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-[(3-hydroxy-1,1-dioxido-2,3-dihydro-1-benzothiophen-5-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 416, Found 416

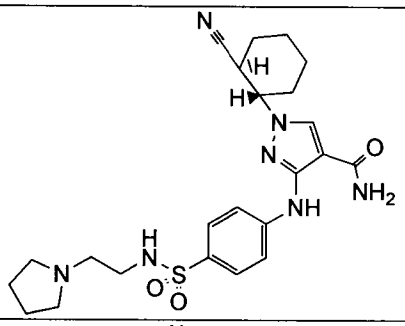
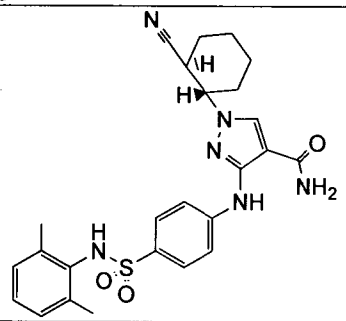
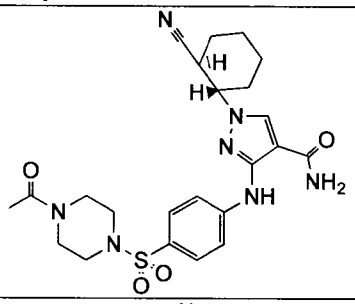
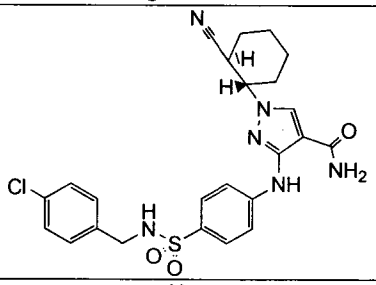
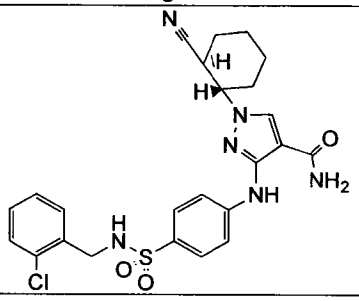
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-63		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-[(1,1-dioxido-1-benzothiophen-5-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 398, Found 398
17-64		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-({4-[(difluoromethyl)sulfonyl]-3-(hydroxymethyl)phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 454, Found 454
17-65		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-({4-[(fluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 406, Found 406
17-66		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-({4-[(cyclopropylmethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 443, found 443
17-67		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-{[4-(pyridin-2-ylsulfamoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 466.0, found 466

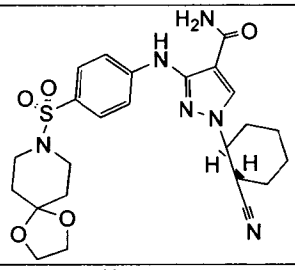
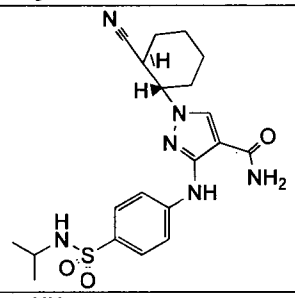
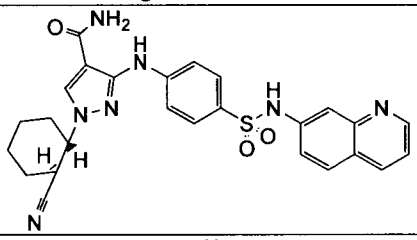
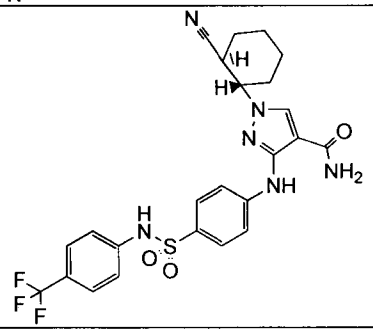
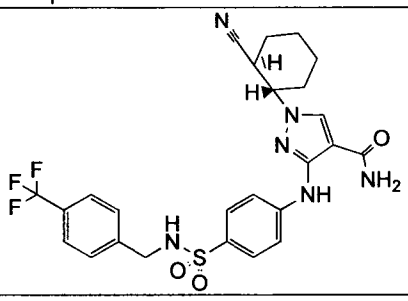
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-68		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-({4-[(2-morpholin-4-ylethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 502, found 502
17-69		3-({4-[(4-benzylpiperidin-1-yl)sulfonyl]phenyl}amino)-1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 547, found 547
17-70		methyl 5-({4-carbamoyl-1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)pyridine-2-carboxylate	Calc'd 369, found 369
17-71		N-tert-butyl-5-({4-carbamoyl-1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)pyridine-3-carboxamide	Calc'd 410, found 410

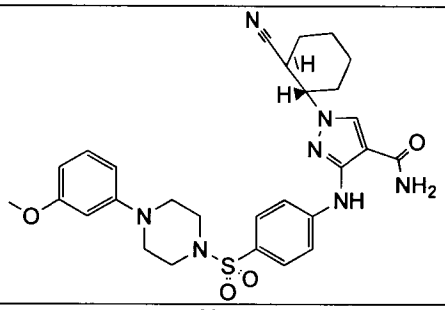
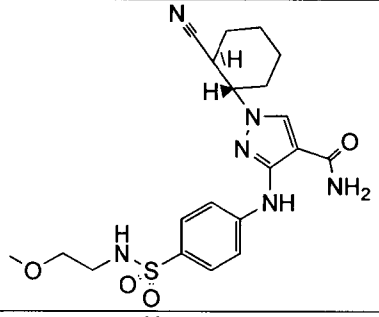
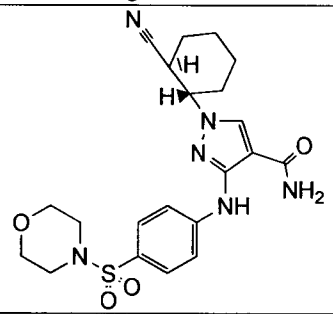
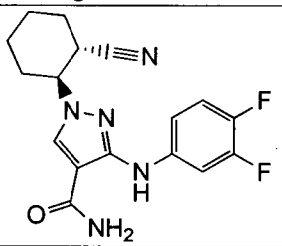
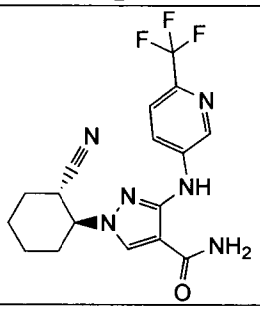
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-72		methyl 5-({4-carbamoyl-1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)pyridine-3-carboxylate	Calc'd 369, found 369
17-73		1-[(1S,2S)-2-cyanocyclohexyl]-3-[(5-methylpyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 325, found 325
17-74		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-[(5-cyanopyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 336, found 336
17-75		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-[(6-cyanopyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 336, found 336
17-76		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-[(7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-b]pyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 366, found 366

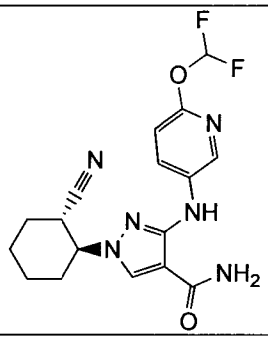
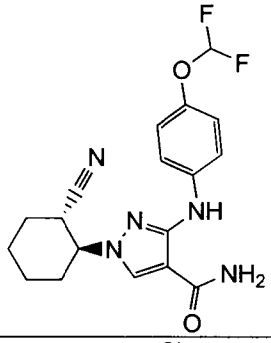
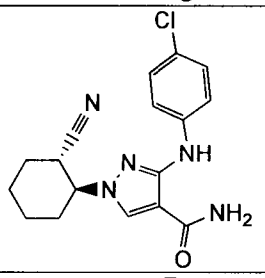
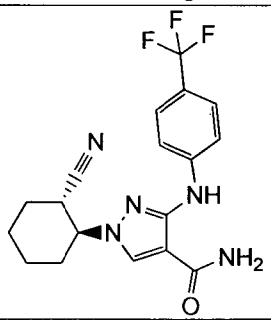
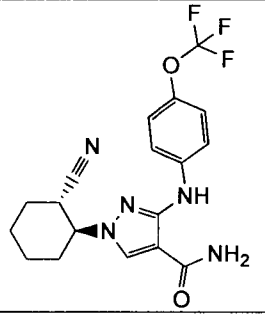
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-77		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-[(6-cyano-5-methylpyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 350, found 350
17-78		methyl 5-({4-carbamoyl-1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)-3-methylpyridine-2-carboxylate	Calc'd 383, found 383
17-79		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-[(6-cyano-5-fluoropyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 354, found 354
17-80		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-[(6-cyclopropylpyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 351, found 351
17-81		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-{[4-(pyridin-4-ylsulfamoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 466, found 466

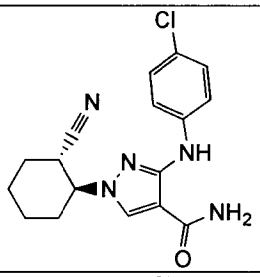
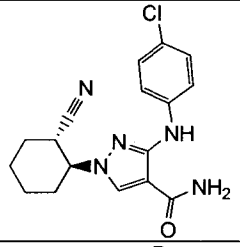
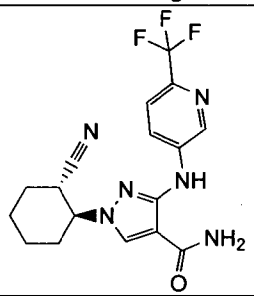
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-82		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-{[4-(cyclohexylsulfamoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 471, found 471
17-83		3-{[4-(benzylsulfamoyl)phenyl]amino}-1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 479, found 479
17-84		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-({4-[(pyridin-3-ylmethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 480, found 480
17-85		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-({4-[(pyridin-2-ylmethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 480, found 480
17-86		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-({4-[(pyridin-4-ylmethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 480, found 480

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-87		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-({4-[(2-pyrrolidin-1-ylethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 486, found 486
17-88		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-({4-[(2,6-dimethylphenyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 493, found 493
17-89		3-({4-[(4-acetylpiperazin-1-yl)sulfonyl]phenyl}amino)-1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 500, found 500
17-90		3-({4-[(4-chlorobenzyl)sulfamoyl]phenyl}amino)-1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 513, found 513
17-91		3-({4-[(2-chlorobenzyl)sulfamoyl]phenyl}amino)-1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 513, found 513

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-92		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-{[4-(1,4-dioxa-8-azaspiro[4.5]dec-8-ylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 515, found 515
17-93		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-({4-[(1-methylethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 431, found 431
17-94		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-{[4-(quinolin-7-ylsulfamoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 516, found 516
17-95		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-[(4-{[4-(trifluoromethyl)phenyl]sulfamoyl}phenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 533, found 533
17-96		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-[(4-{[4-(trifluoromethyl)benzyl]sulfamoyl}phenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 547, found 547

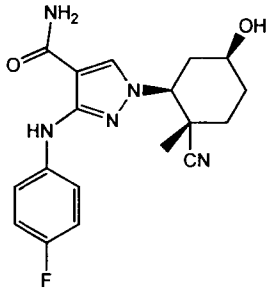
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-97		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-[(4-{[4-(3-methoxyphenyl)piperazin-1-yl]sulfonyl}phenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 564, found 564
17-98		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-({4-[(2-methoxyethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 447, found 447
17-99		1-[(1R,2R or 1S,2S)-2-cyanocyclohexyl]-3-{[4-(morpholin-4-ylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 459, found 459
17-100		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-[(3,4-difluorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 346, found 346
17-101		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 379, found 379

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-102		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 377, found 377
17-103		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-{[4-(difluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 376, found 376
17-104		3-[(4-chlorophenyl)amino]-1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 344, found 344
17-105		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 378, found 378
17-106		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-{[4-(trifluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 394, found 394

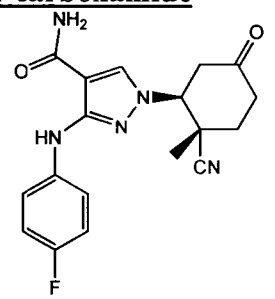
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
17-107		3-[(4-chlorophenyl)amino]-1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 344, found 344
17-108		3-[(4-chlorophenyl)amino]-1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 344, found 344
17-109		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 379, found 379

Scheme #56

Example #18



1-((1S,2S,5S and 1R,2R,5R)-2-Cyano-5-hydroxy-2-methylcyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide



Step A: **1-((1S,2S and 1R,2R)-2-Cyano-2-methyl-5-oxocyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide**

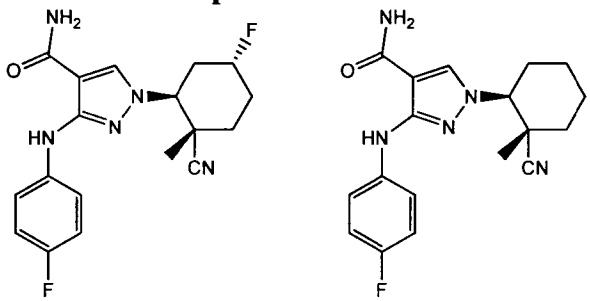
DBU (1.0 mL, 6.7 mmol) was added to a mixture of 1-methyl-4-oxocyclohex-2-enecarbonitrile (1.00 g, 5.18 mmol) and 3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide (**Intermediate #44-7,** 1.14 g, 5.18 mmol) in ethanol (2 mL). The reaction mixture was stirred for 3 hours at 23 °C, and was then adsorbed onto silica gel *in vacuo* and purified by MPLC on silica gel (using a gradient elution of 0 to 10% MeOH/DCM). Desired fractions were identified, combined and concentrated *in vacuo* (23 °C water bath) to afford the title compound. LRMS (ESI) calc'd for $C_{18}H_{19}FN_5O_2$ $[M+H]^+$: 356, Found: 356.

Step B: **1-((1S,2S,5S and 1R,2R,5R)-2-Cyano-5-hydroxy-2-methylcyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide**

Sodium borohydride (10 mg, 0.27 mmol) was added to a solution of 1-((1S,2S and 1R,2R)-2-cyano-2-methyl-5-oxocyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide (48 mg, 0.14 mmol) in THF (0.68 mL) and methanol (0.68 mL) at ambient temperature. The reaction mixture was stirred for 5 minutes at ambient temperature, and then concentrated *in vacuo*. The residue was partitioned between EtOAc and saturated aqueous sodium bicarbonate solution. The organic layer was washed with brine, and the washed solution was dried over anhydrous sodium sulfate. The dried solution was filtered, and the filtrate was concentrated *in vacuo* to afford the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 8.15 (s, 1H), 7.55–7.52 (m, 2H), 6.96 (t, J = 9.0 Hz, 2H), 4.55 (dd, J = 10.5, 5.0 Hz, 1H), 3.83–3.77 (m, 1H), 2.24–1.90 (m, 5H), 1.59–1.51 (m, 1H), 1.30 (s, 3H). LRMS (ESI) calc'd for $C_{18}H_{21}FN_5O_2$ $[M+H]^+$: 358, Found: 358.

Scheme #56

Example #19-1 and 19-2



1-((1S,2S,5R and 1R,2R,5S)-2-cyano-5-fluoro-2-methylcyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide
and 1-((1S,2S and 1R,2R)-2-cyano-2-methylcyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide

BAST (47 mg, 0.21 mmol) was added to a mixture of 1-((1S,2S,5S and 1R,2R,5R)-2-cyano-5-hydroxy-2-methylcyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide (38 mg, 0.11 mmol) in DCM (2.1 mL) at 0 °C. The cooling bath was removed and the reaction mixture was allowed to warm to ambient temperature. 20 minutes after the addition

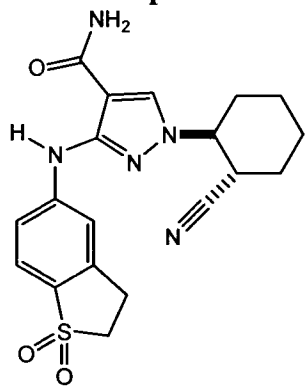
of BAST, the reaction mixture was partitioned between EtOAc and saturated aqueous sodium bicarbonate solution. The organic layer was washed with brine, and the washed solution was dried over anhydrous sodium sulfate. The dried solution was filtered, and the filtrate was concentrated *in vacuo* to afford a mixture of olefin isomers and a fluorinated product. The crude reaction product (36 mg, 0.11 mmol) was dissolved in THF (2.1 mL), and palladium (10% on carbon, 45 mg, 0.040 mmol) was added. The flask was equipped with a three-way adapter with outlets to vacuum and a hydrogen balloon. The reaction mixture was alternately evacuated and filled with hydrogen gas three times, then allowed to stir under hydrogen at ambient temperature for 4 hours. The reaction mixture was filtered through cotton, and the filtrate was concentrated *in vacuo*. The residue was purified by reverse-phase HPLC (using a gradient elution of MeCN/water, with 0.1% v/v TFA modifier). Desired fractions were identified, combined, neutralized with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title compounds.

Example 19-1: First product to elute from reverse phase HPLC; 1-((1S,2S,5R and 1R,2R,5S)-2-cyano-5-fluoro-2-methylcyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide. ^{1}H NMR (500 MHz, CD_3OD): δ 8.15 (s, 1H), 7.51 (dd, J = 9.0, 4.5 Hz, 2H), 6.97 (t, J = 8.7 Hz, 2H), 5.17 (br d, J = 48.0 Hz, 1H), 4.73 (dd, J = 11.0, 4.5 Hz, 1H), 2.60 (dddd, J = 36.0, 14.5, 11.5, 3.0 Hz, 1H), 2.33–2.27 (m, 2H), 2.09–1.93 (m, 3H), 1.39 (s, 3H).
LRMS (ESI) calc'd for $C_{18}H_{20}F_2N_5O$ $[M+H]^+$: 360, Found: 360.

Example 19-2: Second product to elute from reverse phase HPLC; 1-((1S,2S and 1R,2R)-2-cyano-2-methylcyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (s, 1H), 7.71 (s, 1H), 7.51–7.48 (m, 2H), 6.97 (t, J = 8.7 Hz, 2H), 5.56 (br s, 2H), 4.21 (dd, J = 11.0, 3.7 Hz, 1H), 2.35–2.27 (m, 1H), 2.15 (dt, J = 14.0, 3.2 Hz, 1H), 2.06–1.92 (m, 2H), 1.74–1.47 (m, 4H), 1.36 (s, 3H). LRMS (ESI) calc'd for $C_{18}H_{21}FN_5O$ $[M+H]^+$: 342, Found: 342.

Scheme #30

Example #20

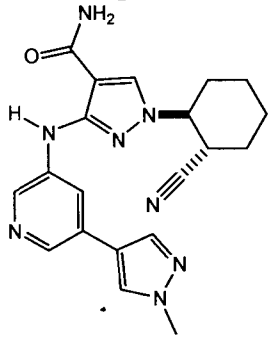


1-[(1S,2S and 1R,2R)-2-Cyanocyclohexyl]-3-[(1,1-dioxido-2,3-dihydro-1-benzothiophen-5-yl)amino]-1*H*-pyrazole-4-carboxamide

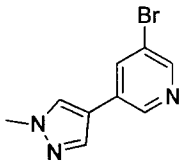
[(1S,2S and 1R,2R)-2-Cyanocyclohexyl]-3-[(1,1-dioxido-1-benzothiophen-5-yl)amino]-1*H*-pyrazole-4-carboxamide (**Example #17-82**, 0.11 g, 0.28 mmol) was dissolved in 1:1 EtOAc:EtOH (55 mL) and added to a Parr shaker. 10 % Palladium on activated carbon (0.03 g, 0.03 mmol) was added and the resulting mixture was subjected to alternating vacuum and H_2 gas (4x). The mixture was then allowed to shake under an atmosphere of H_2 (50 psi) for 1.5 hours. The mixture was then subjected to alternating vacuum and N_2 gas (4x). The mixture was filtered through celite and rinsed with DCM. The filtrate was concentrated *in vacuo*, and the residue was purified by MPLC on silica gel (using a gradient elution of 0-60% EtOAc/hexanes followed by a gradient elution of 0-10% MeOH/DCM). Desired fractions were identified, combined, and concentrated *in vacuo* to afford the title compound, **Example # 20**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.29 (s, 1H), 7.77 (s, 1H), 7.60 (s, 2H), 7.48 (s, 1H), 5.22 (br s, 2H), 4.05-3.95 (m, 1H), 3.48 (t, J = 7.1 Hz, 2H), 3.34 (t, J = 7.1 Hz, 2H), 3.20 – 3.10 (m, 1H), 2.35- 2.28 (m, 1H), 2.15-1.90 (m, 3H), 1.90-1.80 (m, 1H), 1.78-1.64 (m, 1H), 1.50-1.30 (m, 2H). LRMS (ESI) calc'd for $C_{19}H_{21}N_5O_3S$ $[M+H]^+$: 400, Found: 400.

Scheme #24

Example #21-1



1-[(1S,2S or 1R,2R)-2-Cyanocyclohexyl]-3-{[5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide



Step A: **3-Bromo-5-(1-methyl-1*H*-pyrazol-4-yl)pyridine**

3,5-Dibromopyridine (500 mg, 2.11 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (400 mg, 1.9 mmol), 1,1'bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (172 mg, 0.211 mmol), and potassium phosphate tribasic (1.34 g, 6.33 mmol) were combined in a 20 mL microwave vial and dissolved in dioxane (9 mL) and water (1 mL). The vial was sealed and flushed with argon. The reaction mixture was stirred at 90 °C for 2 hours. The vial was then cooled to ambient temperature and diluted with ethyl acetate. The organic layer was washed with water ,brine, and then dried over anhydrous magnesium sulfate. The solution was then filtered and concentrated *in vacuo*. The

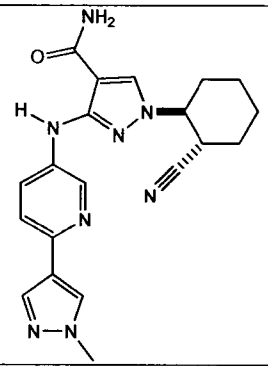
crude material was purified by MPLC on silica gel (using a gradient elution of 0-10% MeOH/DCM) to afford the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.44 (s, 1H), 7.82 (s, 1H), 7.72 (s, 1H), 7.63 (s, 1H), 3.91 (s, 3H). LRMS (ESI) calc'd for $C_9H_8BrN_3$ $[M+H]^+$: 238, Found: 238.

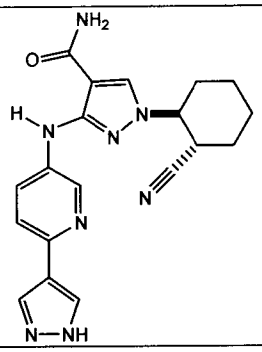
Step B: **1-((1S,2S or 1R,2R)-2-Cyanocyclohexyl)-3-((5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)amino)-1*H*-pyrazole-4-carboxamide**

3-Bromo-5-(1-methyl-1*H*-pyrazol-4-yl)pyridine (51 mg, 0.21 mmol), 3-amino-1-((1S,2S or 1R,2R)-2-cyanocyclohexyl)-1*H*-pyrazole-4-carboxamide (50 mg, 0.21 mmol), $Pd_2(dba)_3$ (20 mg, 0.021 mmol), 2-di-t-butylphosphino-3,4,5,6-teramethyl-2',4',6'-triisopropylbiphenyl (31 mg, 0.064 mmol), and K_3PO_4(136 mg, 0.643 mmol) were combined in a 4 mL vial and mixed with 1,4-dioxane (1.0 mL). The vial was capped and flushed with argon. The reaction was stirred at 90 °C for 16 hours and then cooled to ambient temperature and diluted with ethyl acetate. The organic layer was then washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified using mass-triggered reverse phase preparative HPLC (MeCN/water, with 0.1% v/v TFA modifier) to give the title compound as a trifluoroacetate salt. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.65 (s, 1H), 9.10 (s, 1H), 8.61 (s, 1H), 8.57 (s, 1H), 8.37 (s, 1H), 8.33 (s, 1H), 8.07 (s, 1H), 7.83 (br, 1H), 7.32 (br, 1H), 4.49 – 4.44 (m, 1H), 3.89 (s, 3H), 3.36 – 3.31 (m, 1H), 2.18 – 2.15 (m, 1H), 2.02 – 1.99 (m 1H), 1.89 – 1.70 (m, 4H), 1.50 – 1.42 (m, 1H), 1.35 – 1.28 (m, 1H). LRMS (ESI) calc'd for $C_{20}H_{22}N_8O$ $[M+H]^+$: 391, Found: 391.

The following compounds found in **TABLE 18** were prepared according to **Scheme #26** following similar procedures described for **Example #21-1**, which can be achieved by those of ordinary skill in the art of organic synthesis.

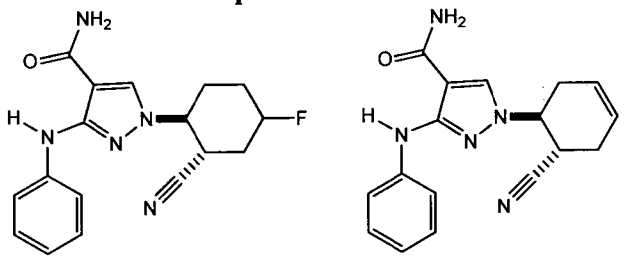
TABLE 18:

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
21-2		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-{[6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 391, Found 391

21-3		1-[(1S,2S and 1R,2R)-2-cyanocyclohexyl]-3-{[6-(1*H*-pyrazol-4-yl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 377, Found 377

Scheme #33

Example #22-1 and 22-2



1-[(1S,2S and 1R,2R)-2-Cyano-4-fluorocyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide and 1-[(1S,6S)-6-cyanocyclohex-3-en-1-yl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide

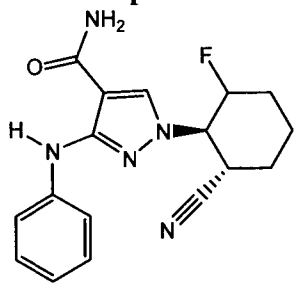
1-[(1S,2S,4R and 1R,2R,4S)-2-Cyano-4-hydroxycyclohexyl]- 3-(phenylamino)-1*H*-pyrazole-4-carboxamide (25 mg, 0.077 mmol) was dissolved in DCM (0.77 mL) and cooled to -78 °C. BAST (0.014 mL, 0.077 mmol) was added to the reaction mixture and it was allowed to stir at -78 °C for 1 hour. The reaction mixture was then partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in DMSO (2 mL) and purified by mass-triggered reverse phase preparative HPLC (MeCN/water, with 0.1% v/v TFA modifier). Desired fractions were identified, combined, and lyophilized to afford the title compounds,

Example #22-1, 1-[(1S,2S and 1R,2R)-2-Cyano-4-fluorocyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide.: ^{1}H NMR (DMSO-d_6): δ 9.15 (br s, 1H), 8.21 (s, 1H), 7.69 (br s, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.23 (dd, J = 7.5, 7.5 Hz. 2H), 7.16 (br s, 1H), 6.82 (dd, J = 7.0, 7.0 Hz, 1H), 4.77 (ddddd, J = 48, 10.5, 10.5, 4.5, 4.5 Hz, 1H), 4.51 (ddd, J = 10.5, 10.5, 5.5 Hz, 1H), 3.53 (dd, J = 11.5, 11.5 Hz, 1H), 2.18-1.90 (m, 5H), 1.70 (m, 1H).
LRMS (ESI) calc'd for $C_{17}H_{18}FN_5O$ $[M+H]^+$: 328, Found: 328.

Example #22-2, 1-[(1S,6S)-6-cyanocyclohex-3-en-1-yl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide: ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.16 (s, 1 H); 8.25 (s, 1 H); 7.69 (s, 1 H); 7.50 (d, J = 8.0 Hz, 2 H); 7.24 (t, J = 7.7 Hz, 2 H); 7.15 (s, 1 H); 6.81 (t, J = 7.3 Hz, 1 H); 5.69-5.73 (m, 2 H); 4.66 (td, J = 10.3, 5.7 Hz, 1 H); 3.52 (td, J = 10.5, 5.9 Hz, 1 H); 2.40-2.70 (m, 4 H).
LRMS (ESI) calc'd for $C_{17}H_{18}FN_5O$ $[M+H]^+$: 308, Found: 308.

Scheme #33

Example #23-1



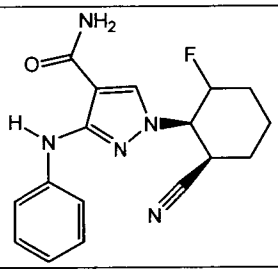
1-[(1*R*,2*S* and 1*S*,2*R*)-2-Cyano-6-fluorocyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide

A solution of 3-anilino-1-[(1R,2S,6R and 1S,2R,6S)-2-cyano-6-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide (**Example #2-6**, 43 mg, 0.13 mmol) in DCM was cooled to 0 °C and allowed to stir. BAST (0.12 mL, 0.66 mmol) was added to the mixture, and then the cooling bath was removed. The reaction mixture was allowed to stir at ambient temperature for 3 hours. The reaction mixture was then partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 60-100%, EtOAc/hexanes) to afford the title compound, **Example #23-1**. ^{1}HNMR (600 MHz, $CDCl_3$): δ 8.66 (s, 1H), 7.69 (d, J = 1.8 Hz, 1H), 7.53 (dd, J = 8.7, 0.9 Hz, 2H), 7.26 (t, J = 8.4Hz, 2H), 6.88 (t, J = 7.5 Hz, 1H), 5.50 (br s, 2H), 5.10-5.01 (m, 1H), 4.40 (ddd, J = 28.2, 12.0, 1.8 Hz, 1H), 3.34 (td, J = 12.0, 3.6 Hz, 1H), 2.38-2.34 (m, 1H), 2.24-2.19 (m, 1H), 1.82 (qd, J = 12.0, 3.9 Hz, 1H), 1.76-1.60 (m, 3H). LRMS (ESI) calc'd for $C_{17}H_{19}FN_5O$ $[M+H]^+$: 328, Found: 328.

The following compounds found in **TABLE 19** were prepared according to **Scheme #33** following similar procedures described for **Example #23-1**, which can be achieved by those of ordinary skill in the art of organic synthesis.

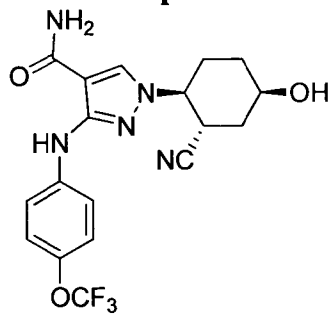
TABLE 19:

Example	Structure	Compound Name	Exact Mass $[M+H]^+$

23-2		1-[(1*R*,2*R* and 1*S*,2*S*)-2-cyano-6-fluorocyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 328, Found 328

Scheme #36

Example #24

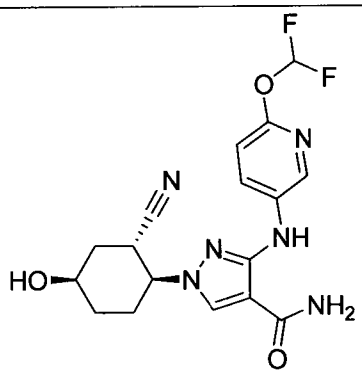
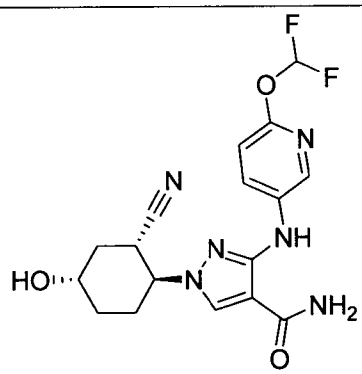
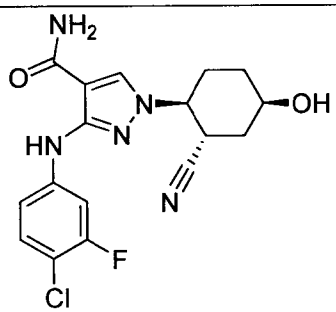


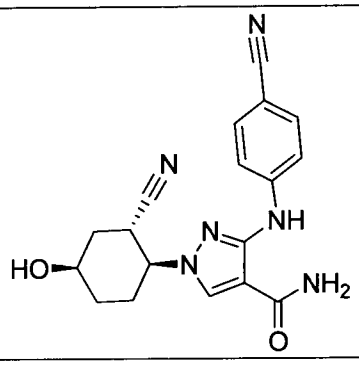
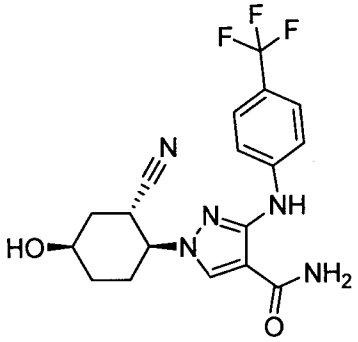
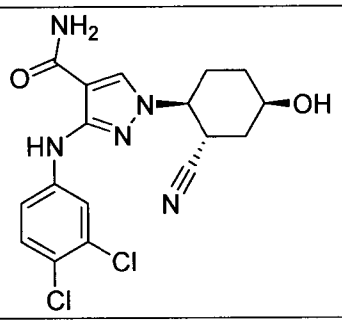
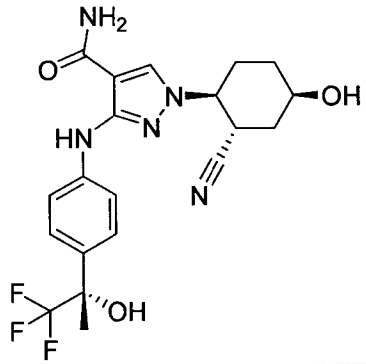
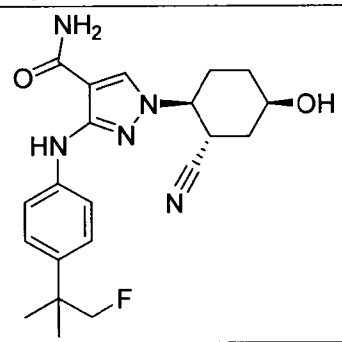
1-((1S,2S or 1R,2R)-2-cyano-4(R)-hydroxycyclohexyl)-3-((4-(trifluoromethoxy)phenyl)amino)-1*H*-pyrazole-4-carboxamide

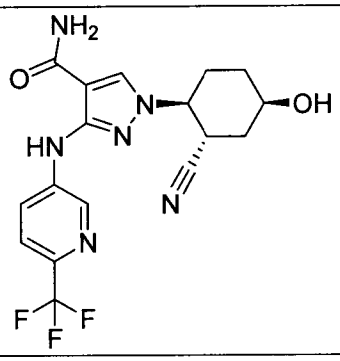
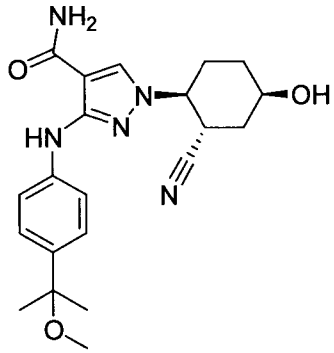
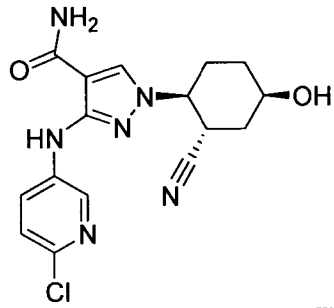
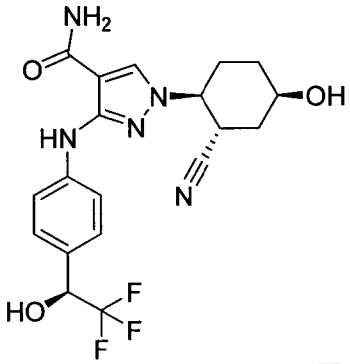
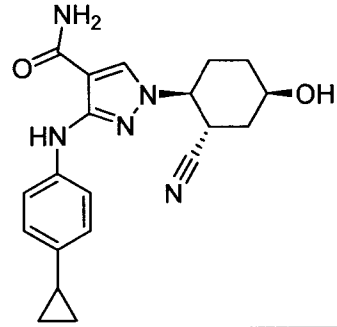
3-Amino-1-((1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl)-1*H*-pyrazole-4-carboxamide (2.5 g, 10.03 mmol), 1-bromo-4-(trifluoromethoxy)benzene (1.79 mL, 12.0 mmol), 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl (1.29 g, 3.01 mmol), and KOAc (2.95 g, 30.1 mmol) were combined in 2-propanol (50.1 mL). Argon was bubbled through the resulting mixture for 10 minutes followed by addition of $Pd_2(dba)_3$ (1.38 g, 1.50 mmol). The flask was then sealed and flushed with more argon. The reaction mixture was stirred at 85 °C for 16 hours. The reaction mixture was cooled to ambient temperature, diluted with EtOAc and scavenged with Quadrapure TU for 2 hours. The mixture was filtered through celite and the filtrate was concentrated *in vacuo*. The crude residue was purified by MPLC (using a gradient elution of 0-10% MeOH/DCM) to afford the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.28 (s, 1H), 8.27 (s,1H), 7.67 (br, 1H), 7.61 – 7.59 (d, 2H), 7.25 – 7.23 (d, 2H), 7.19 (br, 1H), 4.89 (s, 1H), 4.45 – 4.39 (m, 1H), 3.96 (m, 1H), 3.52 – 3.46 (m, 1H), 2.25 – 2.16 (m, 1H), 2.11 – 2.07 (m, 1H), 1.98 – 1.92 (m, 1H), 1.76 – 1.72 (m, 2H), 1.66 – 1.60 (m, 1H). LRMS (ESI) calc'd for $C_{18}H_{18}F_3N_5O_3$ [M+H]+: 410, Found: 410.

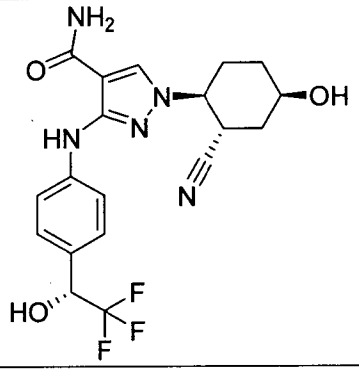
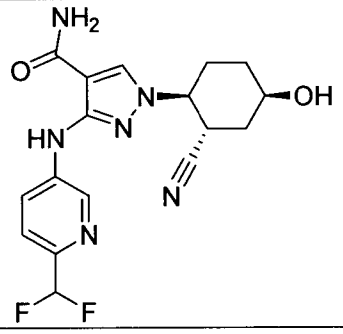
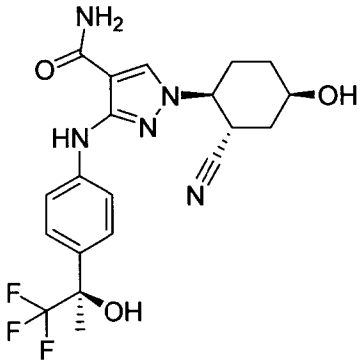
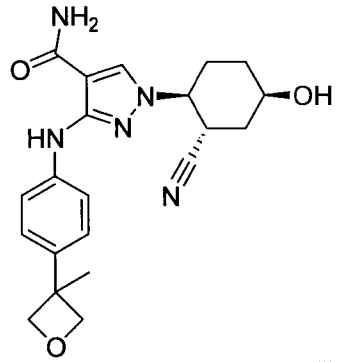
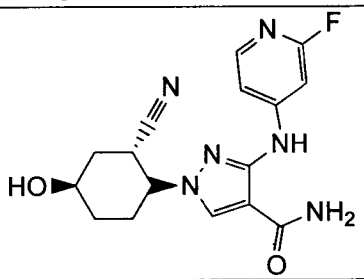
The following compounds found in **TABLE 20** were prepared according to **Scheme #36** following similar procedures described for **Example #24**, which can be achieved by those of ordinary skill in the art of organic synthesis.

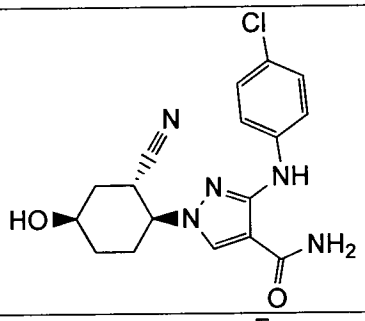
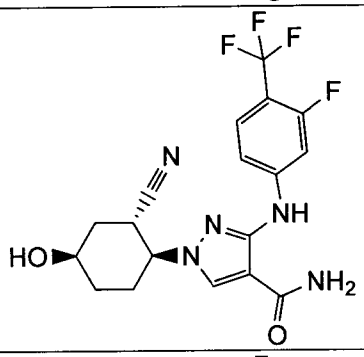
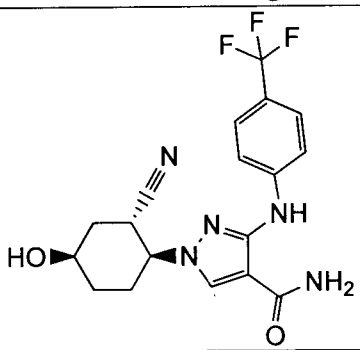
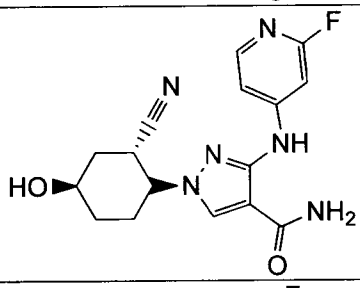
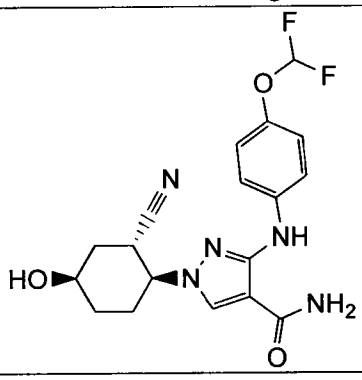
TABLE 20:

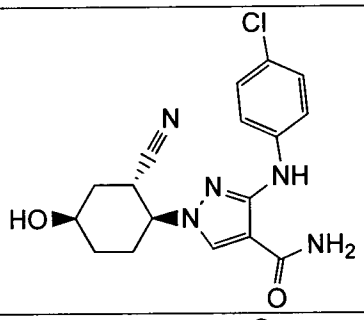
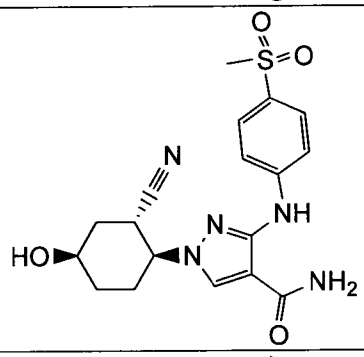
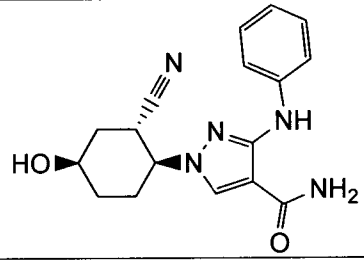
Example	Structure	Compound Name	Exact Mass [M+H]+
25-1		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 393, found 393
25-2		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 393, found 393
25-3		3-[(4-chloro-3-fluorophenyl)amino]-1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 378, found 378

25-4		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-[(4-cyanophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 351, found 351
25-5		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 394, found 394
25-6		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-[(3,4-dichlorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 394, found 394
25-8		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 438, found 438
25-9		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-{[4-(2-fluoro-1,1-dimethylethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 400, found 400

25-10		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 395, found 395
25-11		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-{[4-(1-methoxy-1-methylethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 398, found 398
25-12		3-[(6-chloropyridin-3-yl)amino]-1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 361, found 361
25-13		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 424, found 424
25-14		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-[(4-cyclopropylphenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 366, found 366

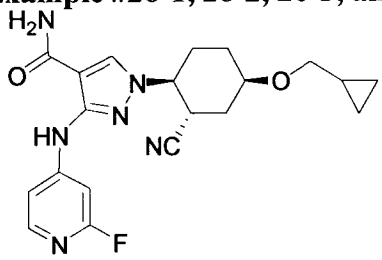
25-15		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 424, found 424
25-16		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-{[6-(difluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 377, found 377
25-17		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-({4-[(1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 438, found 438
25-20		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-{[4-(3-methyloxetan-3-yl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 396, found 396
25-21		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 345, found 345

25-22		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 360, found 360
25-23		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-{[3-fluoro-4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 412, found 412
25-24		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 394, found 394
25-25		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 345, found 345
25-26		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-{[4-(difluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 392, found 392

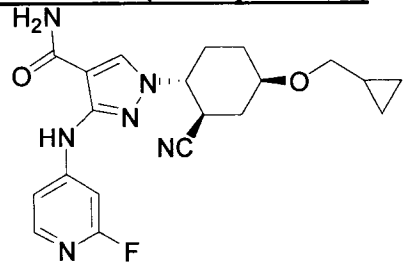
25-27		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 360, found 360
25-28		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 404, found 404
25-29		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 326, found 326

Scheme #51

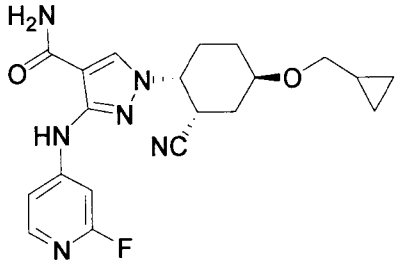
Example #26-1, 26-2, 26-3, and 26-4



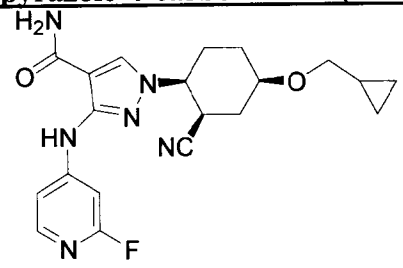
<u>1-[(1*S*,2*S*,4*R* or 1*R*,2*R*,4*S*)-2-Cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide (Example #26-1)</u>



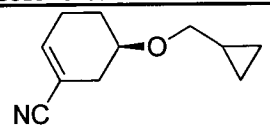
<u>1-[(1*R*,2*R*,4*R* or 1*S*,2*S*,4*S*)-2-Cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide (Example #26-2)</u>



1-[(1*R*,2*S*,4*R* or 1*S*,2*R*,4*R*)-2-Cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide (Example #26-3)

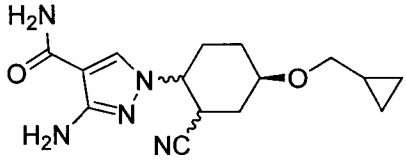


1-[(1S,2R,4R) or (1R,2S,4R)-2-Cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide (Example #26-4)



Step A: **(R or S)-5-(Cyclopropylmethoxy)cyclohex-1-enecarbonitrile**

To the solution of (R or S)-5-Hydroxycyclohex-1-enecarbonitrile (**Intermediate #40**, 2.0 g, 16 mmol) in *N*,*N*-dimethylformamide (10 mL) was added sodium hydride (850 mg, 21 mmol, 60% dispersion in oil) at 0 °C. The resulting suspension was stirred at ambient temperature for 30 minutes before the addition of bromomethylcyclopropane (3.3 g, 24 mmol). The mixture was then stirred at 75 °C for 6 hours, and diluted with EtOAc (50 mL). The organic solution was washed with brine (2x10 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by MPLC on Silica gel (eluting with 2-5 % EtOAc/hexane) to afford the title compound as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 – 6.62 (m, 1H), 3.69 – 3.66 (m, 1H), 3.34 – 3.32 (m, 2H), 2.54 – 2.49 (m, 1H), 2.38 – 2.30 (m, 1H), 2.29 – 2.24 (m, 2H), 1.85 – 1.83 (m, 1H), 1.75 – 1.72 (m, 1H), 1.08 – 1.04 (m, 1H), 0.59 – 0.54 (m, 2H), 0.24 – 0.20 (m, 2H).



Step B: **3-Amino-1-((4R or 4S)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl)-1*H*-pyrazole-4-carboxamide**

A solution of (*R* or S)-5-(cyclopropylmethoxy)cyclohex-1-ene-1-carbonitrile (800 mg, 4.5 mmol), 3-amino-1*H*-pyrazole-4-carboxamide (1.1 g, 8.9 mmol) and DBU (1.4 g, 9.0

mmol) in ethanol (8 mL) was refluxed under nitrogen overnight, and then concentrated *in vacuo*. The crude residue was purified by MPLC on Silica gel (eluting with 1-2 %MeOH/DCM) to afford the title compound as a mixture of diastereomers. MS ESI: $[M+H]^+$ *m/z* 304.

Step C: 1-[(1*S*,2*S*,4*R* or 1*R*,2*R*,4*S*)-2-Cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide *and* **1-[(1*R*,2*R*,4*R* or 1*S*,2*S*,4*S*)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide** *and* **1-[(1*R*,2*S*,4*R* or 1*S*,2*R*,4*R*)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide** *and* **1-[(1S,2R,4R) or (1R,2S,4R)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide**

A mixture of 3-amino-1-((4R or 4S)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl)-1*H*-pyrazole-4-carboxamide (860 mg, 2.8 mmol), 4-bromo-2-fluoropyridine (490 mg, 2.8 mmol), KOAc (550 mg, 5.6 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (290 mg, 0.28 mmol) and *t*-Bu X-Phos (240 mg, 0.57 mmol) in 2-propanol (8 mL) was degassed with bubbling nitrogen for 15 minutes, then stirred at 60 °C for 2 hours under nitrogen. The mixture was cooled to ambient temperature and concentrated *in vacuo*. The crude residue was purified by MPLC on Silica gel (eluting with 1-2 % MeOH/DCM) to afford the title compound as a mixture of 4 diastereomers. This mixture was then separated by preparative reverse-phase HPLC (using a gradient elution of 40-60 % MeCN /water with 0.05 % $NH_3 \cdot H_2O$) to afford the major isomer 1-[(1*S*,2*S*,4*R* or 1*R*,2*R*,4*S*)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide (**Example #26-1**) as an off-white solid, the minor isomer 1-[(1*R*,2*R*,4*R* or1*S*,2*S*,4*S*)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide (**Example #26-2**) as an off-white solid, and a mixture containing the remaining 2 diastereomers.. This mixture was further resolved to the constituent diastereomers via preparative chiral HPLC (Chiralpak IC, 2x25cm; Mobile phase: 50 % EtOH/hexane with 0.1 % TEA) to afford 1-[(1*R*,2*S*,4*R* or 1*S*,2*R*,4*R*)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide (**Example 26-3**) and 1-[(1*S*,2*R*,4*R* or 1*R*,2*S*,4*R*)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide (**Example 26-4**).

Example 26-1: 1-[(1*S*,2*S*,4*R* or 1*R*,2*R*,4*S*)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide: ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 7.92 (d, *J* = 6.0 Hz, 1H), 7.50 (s, 1H), 7.22 (d, *J* = 5.6 Hz, 1H), 4.41 – 4.39 (m, 1H), 3.80 – 3.78 (m, 1H), 3.67 – 3.61 (m, 1H), 3.41 – 3.33 (m, 2H), 2.48 – 2.39 (m, 2H), 2.17 – 2.13 (m, 1H), 2.00 – 1.89 (m, 2H), 1.67 – 1.66 (m, 1H), 1.16 – 1.13 (m, 1H), 0.63 – 0.58 (m, 2H), 0.34 – 0.30 (m, 2H). MS ESI: $[M+H]^+$ *m/z* 399.

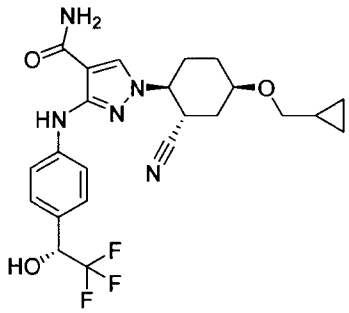
Example 26-2: 1-[(1*R*,2*R*,4*R* or 1*S*,2*S*,4*S*)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide: ^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (s, 1H), 7.92 (d, *J* = 6.0 Hz, 1H), 7.43 (s, 1H), 7.25 (d, *J* = 6.0 Hz, 1H), 4.41 – 4.39 (m, 1H), 3.60 – 3.46 (m, 2H), 3.43 – 3.32 (m, 2H), 2.60 – 2.57 (m, 1H), 2.26 – 2.13 (m, 3H), 1.78 – 1.72 (m, 1H), 1.69 – 1.50 (m, 1H), 1.10 – 1.06 (m, 1H), 0.58 – 0.54 (m, 2H), 0.27 – 0.23 (m, 2H). MS ESI: $[M+H]^+$ *m/z* 399.

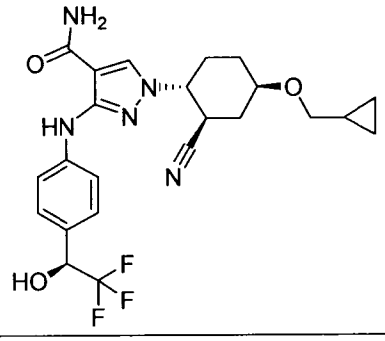
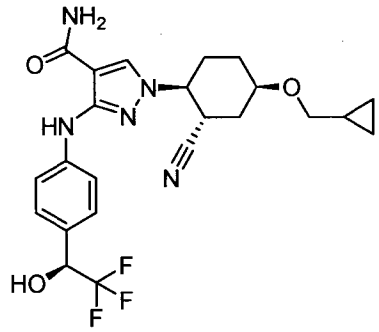
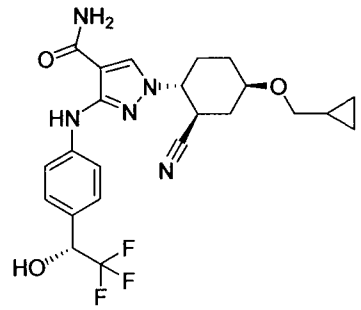
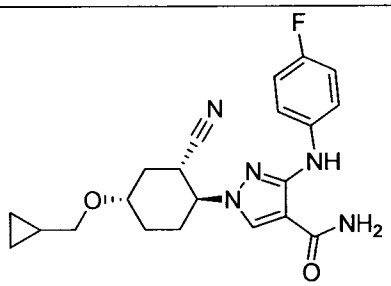
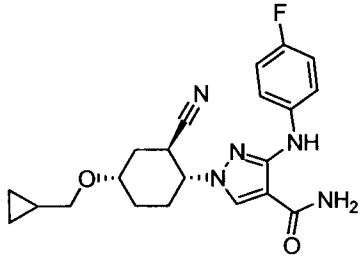
Example 26-3: 1-[(1*R*,2*S*,4*R* or 1*S*,2*R*,4*S*)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide: ^{1}H NMR (300 MHz, CD_3OD) δ 8.21 (s, 1H), 7.94 (d, *J* = 6.0 Hz, 1H), 7.52 (s, 1H), 7.27 (d, *J* = 6.0 Hz, 1H), 4.56 – 4.52 (m, 1H), 3.80 – 3.78 (m, 2H), 3.55 – 3.34 (m, 2H), 2.57 – 2.49 (m, 2H), 2.26 – 2.25 (m, 1H), 2.31 – 1.97 (m, 2H), 1.83 – 1.73 (m, 1H), 1.14 – 1.12 (m, 1H), 0.58 – 0.53 (m, 2H), 0.39 – 0.30 (m, 2H). MS ESI: $[M+H]^+$ *m/z* 399.

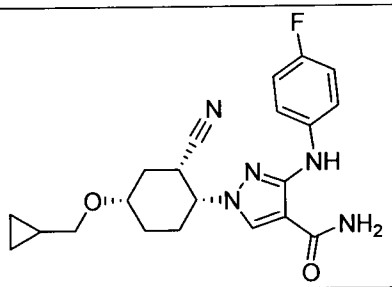
Example 26-4: 1-[(1*S*,2*R*,4*R* or 1*R*,2*S*,4*S*)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide: ^{1}H NMR (300 MHz, CD_3OD) δ 8.38 (s, 1H), 7.86 (d, *J* = 6.0 Hz, 1H), 7.46 (s, 1H), 7.21 (d, *J* = 6.0 Hz, 1H), 4.49 – 4.46 (m, 1H), 3.85 – 3.84 (m, 1H), 3.71 – 3.62 (m, 1H), 3.39 – 3.37 (m, 2H), 2.44 – 2.40 (m, 1H), 2.30 – 2.22 (m, 3H), 1.85 – 1.77 (m, 1H), 1.58 – 1.47 (m, 1H), 1.03 – 1.00 (m, 1H), 0.53 – 0.48 (m, 2H), 0.24 – 0.19 (m, 2H). MS ESI: $[M+H]^+$ *m/z* 399.

The following compounds found in **TABLE 21** were prepared according to **Scheme #51** following similar procedures described for **Example #26-1-4**, which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 21:

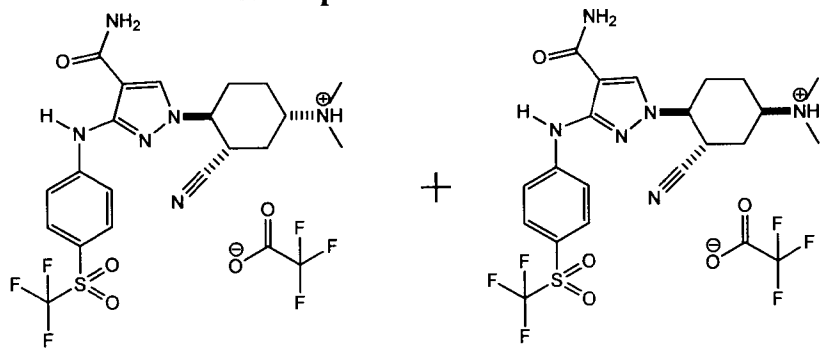
Example	Structure	Compound Name	Exact Mass [M+H]+
26-5		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 478, found 478

Example	Structure	Compound Name	Exact Mass [M+H]+
26-6		1-[(1R,2R,4R or 1S,2S,4S)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 478, found 478
26-7		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 478, found 478
26-8		1-[(1R,2R,4R or 1S,2S,4S)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 478, found 478
26-9		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 398, found 398
26-10		1-[(1R,2R,4S or 1S,2S,4R)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 398, found 398

Example	Structure	Compound Name	Exact Mass [M+H]+
26-11		1-[(1R,2S,4S or 1S,2R,4R)-2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 398, found 398

Scheme #40

Example #27-1 and #27-2



1-[(1S,3S,4S and 1R,3R,4R)-4-[4-carbamoyl-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazol-1-yl]-3-cyano-N,N-dimethylcyclohexanaminium trifluoroacetate *and* **1-[(1R,3S,4S and 1S,3R,4R)-4-[4-carbamoyl-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazol-1-yl]-3-cyano-N,N-dimethylcyclohexanaminium trifluoroacetate**

1-[(1S,2S,4R and 1R,2R,4S)-2-Cyano-4-hydroxycyclohexyl]- 3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide (0.40 g, 0.87 mmol) was dissolved in DCM (2.19 mL):MeCN (2.19 mL). NMO (242 mg, 1.79 mmol) and 4Å molecular sieves (200 mg/mmol) were added and the reaction mixture was allowed to stir at ambient temperature for 15 minutes. TPAP (62 mg, 0.17 mmol) was added to the reaction mixture and it was allowed to stir at ambient temperature for 1 hour. The reaction mixture was then purified directly by MPLC on silica gel (using a gradient elution of 80-100%, EtOAc/hexanes). Desired fractions were identified, combined, and concentrated *in vacuo*. The residue was dissolved in MeOH (0.33 mL) and THF (0.33 mL). Dimethylamine (0.33 mL, 0.66 mmol, 2.0 M in THF), acetic acid (0.034 mL, 0.66 mmol) and sodium cyanoborohydride (10 mg, 0.16 mmol) were then added sequentially at ambient temperature. The resulting mixture was allowed to stir at ambient

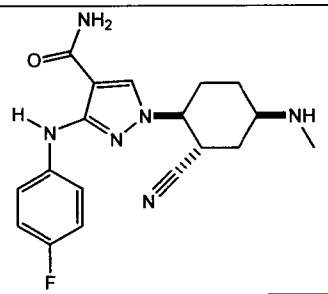
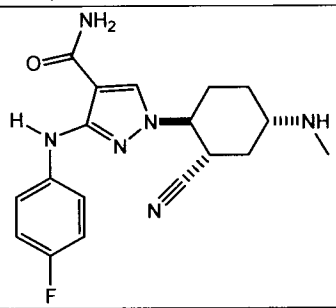
temperature for 18 hours before the reaction mixture was concentrated *in vacuo*. The residue was purified by reverse-phase preparative HPLC (using a gradient elution of MeCN/water, with 0.1% v/v TFA modifier). Desired fractions were identified, combined, and lyophilized to afford the title compounds:

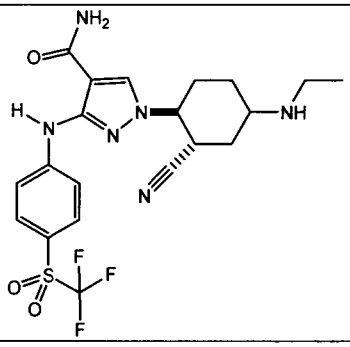
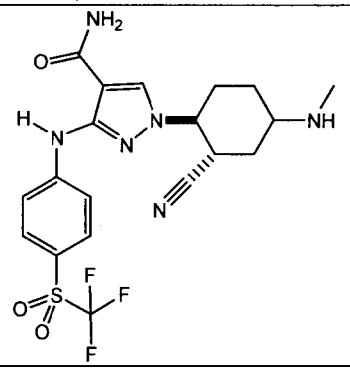
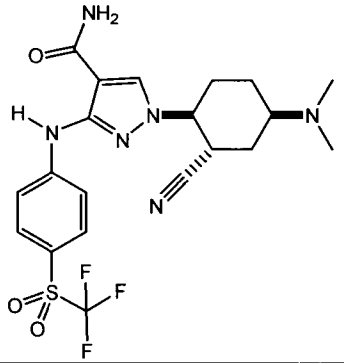
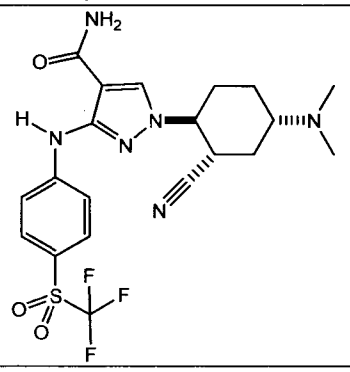
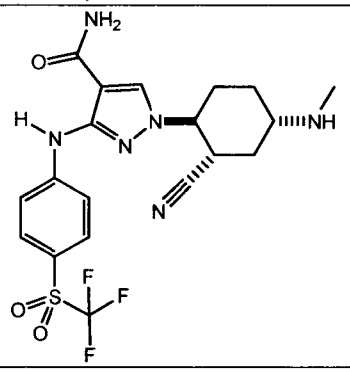
Example #27-1: 1-[(1S,3S,4S and 1R,3R,4R)-4-[4-carbamoyl-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazol-1-yl]-3-cyano-N,N-dimethylcyclohexanaminium trifluoroacetate. ^{1}HNMR (500 MHz, DMSO-d_6): δ 9.98 (s, 1H), 9.53 (s, 1H), 8.41 (s, 1H), 7.92-7.86 (m, 4H), 7.81 (s, 1H), 7.39 (s, 1H), 4.71-4.66 (m, 1H), 4.04-3.99 (m, 1H), 3.49-3.45 (m, 1H), 2.86 (d, J = 4.5 Hz, 3H), 2.81 (d, J = 4.0 Hz, 3H), 2.30-2.19 (m, 3H), 2.11-1.97 (m, 3H). LRMS (ESI) calc'd for $C_{20}H_{23}F_3N_6O_3S$ $[M+H]^+$: 485, Found: 485.

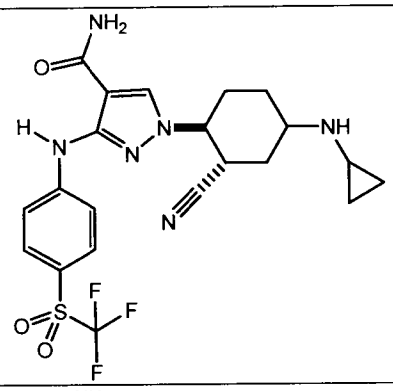
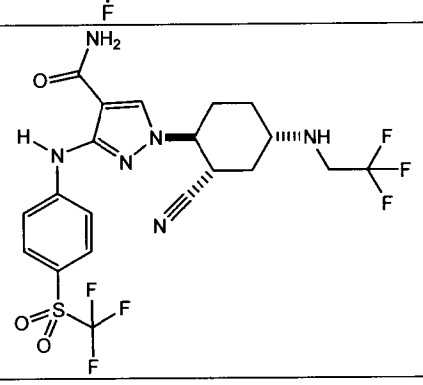
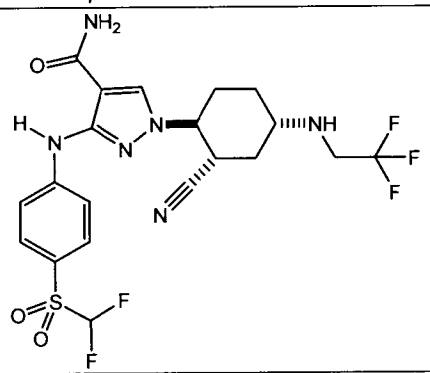
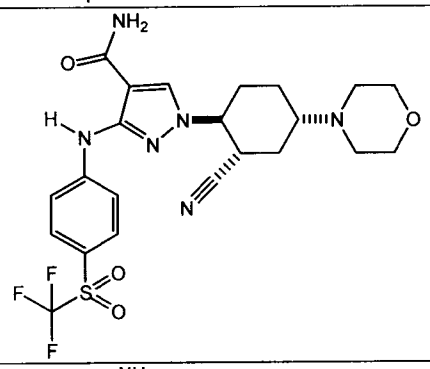
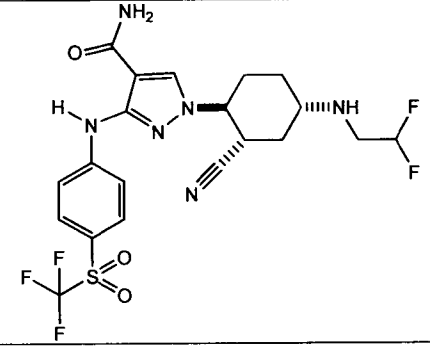
Example #27-2: 1-[(1R,3S,4S and 1S,3R,4R)-4-[4-carbamoyl-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazol-1-yl]-3-cyano-N,N-dimethylcyclohexanaminium trifluoroacetate ^{1}HNMR (500 MHz, DMSO-d_6): δ 10.0 (s, 1H), 9.91 (s, 1H), 8.33 (s, 1H), 7.93-7.85 (m, 5H), 7.39 (s, 1H), 4.57 (td, 11.5, 3.7 Hz, 1H), 3.61 (td, J = 12.0, 3.3 Hz, 1H), 3.45-3.38 (m, 1H), 2.82-2.76 (m, 6H), 2.17-1.97 (m, 5H), 1.72 (m, 1H). LRMS (ESI) calc'd for $C_{20}H_{23}F_3N_6O_3S$ $[M+H]^+$: 485, Found: 485.

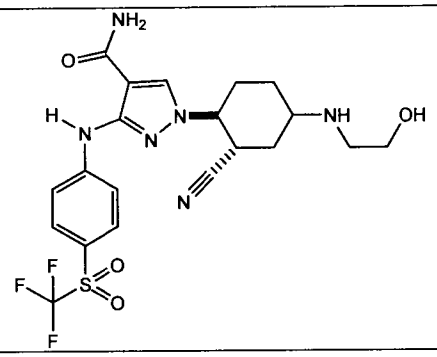
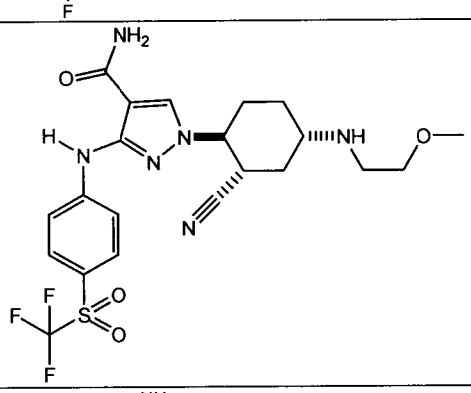
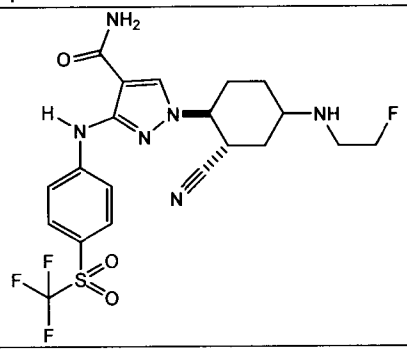
The following compounds shown in **TABLE 22** were prepared according to **Scheme #40** following similar procedures described for **Example #27-1 and 27-2**, which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 22:

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
27-3		**1-[(1S,2S,4R and 1R,2R,4S)-2-cyano-4-(methylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide**	**Calc'd 357, Found 357**
27-4		**1-[(1S,2S,4S and 1R,2R,4R)-2-cyano-4-(methylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide**	**Calc'd 357, Found 357**

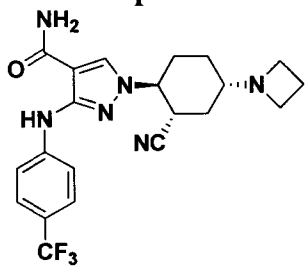
27-5		1-[(1S,2S and 1R,2R)-2-cyano-4-(ethylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 485, Found 485
27-6		1-[(1S,2S and 1R,2R)-2-cyano-4-(methylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 471, Found 471
27-7		1-[(1S,2S,4R and 1R,2R,4S)-2-cyano-4-(dimethylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 485, Found 485
27-8		1-[(1S,2S,4S and 1R,2R,4R)-2-cyano-4-(dimethylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 485, Found 485
27-9		1-[(1S,2S,4S and 1R,2R,4R)-2-cyano-4-(methylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 471, Found 471

27-10		1-[(1S,2S and 1R,2R)-2-cyano-4-(cyclopropylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 497, Found 497
27-11		1-{(1S,2S,4S and 1R,2R,4R)-2-cyano-4-[(2,2,2-trifluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 539, Found 539
27-12		1-{(1S,2S,4S and 1R,2R,4R)-2-cyano-4-[(2,2,2-trifluoroethyl)amino]cyclohexyl}-3-({4-[(difluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 521, Found 521
27-13		1-[(1S,2S,4S and 1R,2R,4R)-2-cyano-4-(morpholin-4-yl)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide	Calc'd 527, Found 527
27-14		1-{(1S,2S,4S and 1R,2R,4R)-2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide	Calc'd 521, Found 521

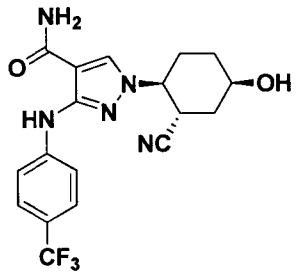
27-15		1-{(1S,2S and 1R,2R)-2-cyano-4-[(2-hydroxyethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide	Calc'd 501, Found 501
27-16		1-{(1S,2S,4S and 1R,2R,4R)-2-cyano-4-[(2-methoxyethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide	Calc'd 515, Found 515
27-17		1-{(1S,2S and 1R,2R)-2-cyano-4-[(2-fluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide	Calc'd 503, Found 503

Scheme #54

Example #28-1

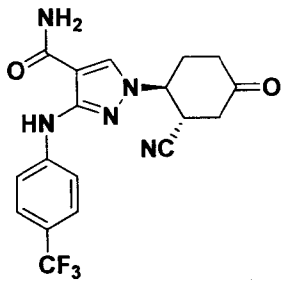


1-{(1S,2S and 1R,2R)-2-cyano-4-[(2-fluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide;



Step A: **1-((1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl)-3-((4-(trifluoromethyl)phenyl)amino)-1*H*-pyrazole-4-carboxamide**

A mixture of 3-amino-1-((1*S*,2*S* and 1*R*,2*R*)-2-cyano-4-hydroxycyclohexyl)-1*H*-pyrazole-4-carboxamide (**Intermediates 48-1** and **48-2**, 150 g, 602 mmol), 4-bromobenzotrifluoride (0.101 L, 722 mmol), $Pd_2(dba)_3$ (27.6 g, 30.1 mmol), 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl (28.1 g, 66.2 mmol), and potassium acetate (89 g, 903 mmol) in 2-propanol (1.5 L) was degassed and stirred at 80 °C for 2.5 hours. After cooling to ambient temperature, the reaction mixture was diluted with 1 L of EtOAc, stirred for 30 minutes, filtered through a celite pad and washed with EtOAc (500 mLx2). The filtrate was adsorbed on silica gel *in vacuo* and purified by column chromatography on silica gel (eluting with 0-8% MeOH/DCM) to give 1-((1*S*,2*S*,4*R* and 1*R*,2*R*,4*S*)-2-cyano-4-hydroxycyclohexyl)-3-((4-(trifluoromethyl)phenyl)amino)-1*H*-pyrazole-4-carboxamide as a pale yellow solid. This racemic mixture was chirally resolved via Chiral SFC column chromatography (Chiral Technology OZ-H 2.1 X 25cm, 5uM) to afford the title compound as the second enantiomer to elute, **Intermediate A of Example 28-1**. ^{1}H NMR (400 MHz, CD_3OD) δ 1.73 (1H, t, *J* = 14. Hz), 1.87-1.85 (1H, m), 1.98-1.96 (2 H, m), 2.25 (1 H, dd, *J* = 14, 3.5 Hz), 2.46 (1H, qd, *J* = 13, 3.6 Hz), 3.68-3.65 (1H, m), 4.10 (1H, s), 4.30 (1H, td, *J* = 11.5, 3.9 Hz), 7.50 (2H, d, *J* = 8.4 Hz), 7.67 (2 H, d, *J* = 8.4 Hz), 8.14 (1 H, s). MS ESI: $[M+H]^+$ *m/z* 394.



Step B : **1-((1*S*,2*S* *or* 1*R*,2*R*)-2-Cyano-4-oxocyclohexyl)-3-((4-(trifluoromethyl)phenyl)amino)-1*H*-pyrazole-4-carboxamide**

To a solution of 1-((1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl)-3-((4-(trifluoromethyl)phenyl)amino)-1*H*-pyrazole-4-carboxamide (61.2 g, 156 mmol) in DMSO (612 mL) was added TEA (65.1 mL, 467 mmol), followed by sulfur trioxide-pyridine complex (74.3 g, 467 mmol) in one portion at ambient temperature (slightly exothermic). The reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was diluted with EtOAc

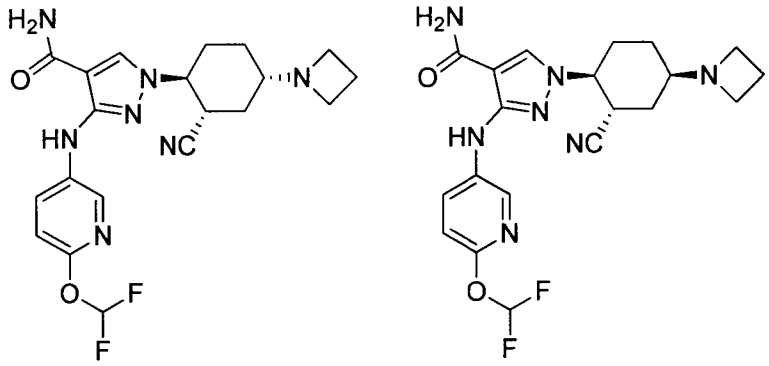
(3000 mL), washed sequentially with saturated aqueous $NaHCO_3$ (1500 mL), water (1000 mL) and brine (500 mLx2). The aqueous layer was back extracted with EtOAc (500 mLx2), and the combined organic layers were then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 0-8% MeOH/DCM) to give the title compound as an off-white solid. ^{1}H NMR (400 MHz, Acetone-d_6) δ 2.41-2.40 (1H, m), 2.53-2.51 (1H, m), 2.61 (1H, tdd, J = 13.4, 11.1, 4.48 Hz), 2.79 (2H, m), 3.00 (1H, dd, J = 15., 13 Hz), 4.07-4.06 (1H, m), 5.04 (1 H, td, J = 10.9, 4. Hz), 6.65 (1 H, br s), 7.30 (1H, br s), 7.54 (2H, d, J = 8.5 Hz), 7.79 (2H, d, J = 8.5 Hz), 8.36 (1H, s), 9.61 (1H, s). MS ESI: $[M+H]^+$ *m/z* 392;

Step C: **1-((1S,2S,4S or 1R,2R,4R)-4-(azetidin-1-yl)-2-cyanocyclohexyl)-3-((4-(trifluoromethyl)phenyl)amino)-1*H*-pyrazole-4-carboxamide**

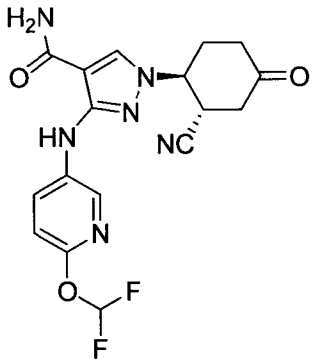
To a solution of 1-((1S,2S or 1R,2R)-2-cyano-4-oxocyclohexyl)-3-((4-(trifluoromethyl)phenyl)amino)-1*H*-pyrazole-4-carboxamide (54.0 g, 138 mmol) and azetidine hydrochloride (38.7 g, 414 mmol) in MeOH (540 mL) was added TEA (57.7 mL, 414 mmol), and acetic acid (118 mL, 2070 mmol), followed by sodium triacetoxyborohydride (58.5 g, 276 mmol) at 0 °C in two portions (slightly exothermic). The reaction mixture was then stirred at 0 °C for 2 hours. After removal of all the volatiles *in vacuo*, the residue was diluted with EtOAc (1500 mL) and basified with saturated aqueous Na_2CO_3. A white precipitate formed and was filtered. The filtrate was partitioned and the aqueous layer was extracted with EtOAc (300 mLx2) . The combined EtOAc layers were washed with brine, dried over anhydrous sodium sulfate, and filtered. The white precipitate was slurried in MeOH (300 mL) for 15 minutes and filtered again. The MeOH filtrate was combined with the EtOAc layer and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 0-10% MeOH/EtOAc with 3 vol% aqueous NH_4OH) to give the title compound as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.12-1.10 (1H, m), 1.37 (1H, q, J = 12 Hz), 1.75 (1 H, d, J = 12. Hz), 1.93-1.85 (4H, m), 2.11-2.07 (2H, m), 3.07 (4H, t, J = 7 Hz), 3.33 (1H, td, J =8 Hz), 4.41 (1H, td, J = 11, 4.08 Hz), 7.21 (1H, br s), 7.54 (2H, d, J = 8 Hz), 7.67 (2H, d, J = 8 Hz), 7.72 (1H, br s), 8.22 (1H, s), 9.49 (1H, s). MS ESI: $[M+H]^+$ *m/z* 433.

Scheme #36 and 41

Example #28-2 and #28-3



1-[(1S,2S,4R or 1R,2R,4S)-4-(Azetidin-1-yl)-2-cyanocyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide *and* **1-[(1S,2S,4S or 1R,2R,4R)-4-(azetidin-1-yl)-2-cyanocyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide**



Step A: **1-[(1S,2S or 1R,2R)-2-Cyano-4-oxocyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide**

To a solution of 1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide (**Example #25-26,** 386 mg, 0.984 mmol) in DMSO (2 mL) was added stabilized 2-iodoxybenzoic acid (413 mg, 1.48 mmol). The resulting slurry was heated to 50 °C for 5 hours. The reaction mixture was cooled to ambient temperature, diluted with EtOAc and washed with saturated aqueous sodium thiosulfate. The organic layer was collected, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford the title compound, (**Intermediate A of Example #28-2**). LRMS (ESI) calc'd for $C_{17}H_{17}F_2N_6O_3$ $[M+H]^+$: 391, Found: 391 + $[M+H_2O]^+$: 409.

Step B: **1-[(1S,2S,4R or 1R,2R,4S)-4-(Azetidin-1-yl)-2-cyanocyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide** *and* **1-[(1S,2S,4S or 1R,2R,4R)-4-(azetidin-1-yl)-2-cyanocyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide**

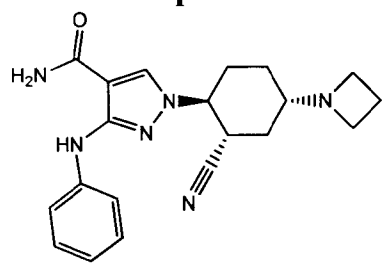
To a solution of 1-[(1S,2S or 1R,2R)-2-cyano-4-oxocyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide (**Intermediate A of Example #28-2,** 100 mg, 0.256 mmol) in THF (1 mL) and MeOH (1 mL) were added azetidine hydrogen chloride salt (240 mg, 2.56 mmol) and triethylamine (0.357 mL, 2.56 mmol). The reaction mixture was stirred for 10 minutes, then acetic acid (0.147 mL, 2.56 mmol) was added. The mixture was stirred for another 10 minutes then sodium cyanoborohydride (40 mg, 0.64 mmol) was added and stirring continued for 14 hours. The reaction mixture was filtered, and the filtrate was purified directly by reverse phase HPLC (using a gradient elution of MeCN/water with 0.1%TFA) to afford the title compounds.

Example #28-2: 1-[(1S,2S,4R or 1R,2R,4S)-4-(azetidin-1-yl)-2-cyanocyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide. ^{1}H NMR (500 MHz, CD_3OD): δ 8.53 (d, J = 3 Hz, 1H), 8.17 (s, 1 H), 8.12-8.09 (dd, J = 9, 3 Hz, 1H), 7.55-7.25 (t, J = 74 Hz, 1H), 6.93 (d, J = 9 Hz, 1 H), 4.30-4.25 (td, J = 11, 4 Hz, 1 H), 3.68-3.63 (td, J = 11, 3 Hz, 1 H), 3.30-3.29 (m, 4H), 2.60 (m, 1 H), 2.33-2.30 (1H), 2.14-2.09 (m, 3H), 1.90-1.811 (m, 3H), 1.62 (m, 1H). LRMS (ESI) calc'd for $C_{20}H_{24}F_2N_7O_2$ $[M+H]^+$: 432, Found: 432

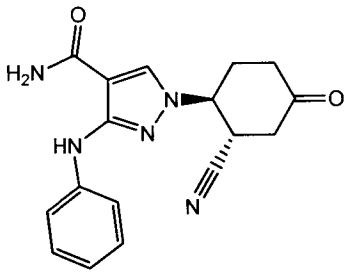
Example #28-3: 1-[(1S,2S,4S or 1R,2R,4R)-4-(azetidin-1-yl)-2-cyanocyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide. ^{1}H NMR (500 MHz, CD_3OD): δ 8.51 (d, J = 3 Hz, 1H), 8.13 (s, 1H), 8.07-8.05 (dd, J = 9, 3 Hz, 1H), 7.38 (t, J = 74 Hz, 1H), 6.89 (d, J = 9 Hz, 1H), 4.30 (m, 1H), 3.46-3.42 (m, 5H), 2.50 (m, 1H), 2.35 (m, 1H), 2.17-2.09 (m, 4H), 2.00 (m, 1H), 1.50-1.48 (m, 1H), 1.251 (m, 1H). LRMS (ESI) calc'd for $C_{20}H_{24}F_2N_7O_2$ $[M+H]^+$: 432, Found: 432.

Scheme #36 and 42

Example #28-4



1-((1R,2R,4R or 1S,2S,4S)-4-(Azetidin-1-yl)-2-cyanocyclohexyl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide



Step A: **1-((1R,2R or 1S,2S)-2-Cyano-4-oxocyclohexyl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide**

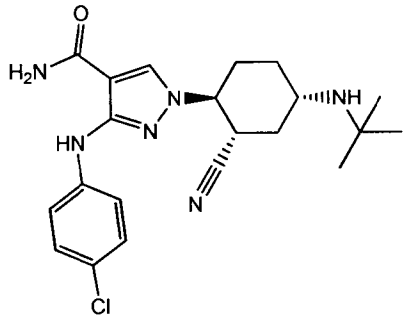
The title compound was prepared using methods similar to those described for the preparation of **Intermediate A of Example #28-2**; using 1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide **(Example #25-29)** as a starting material. LRMS (ESI) calc'd for $C_{17}H_{17}N_5O_2$ $[M+H]^+$: 324, Found: 324.

Step B: **1-((1R,2R,4R or 1S,2S,4S)-4-(Azetidin-1-yl)-2-cyanocyclohexyl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide**

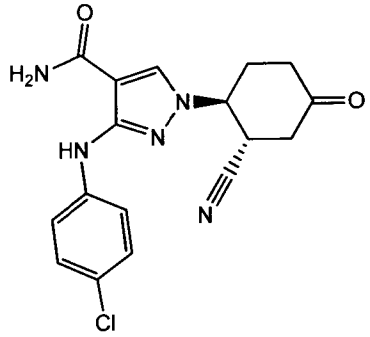
1-((1R,2R or 1S,2S)-2-Cyano-4-oxocyclohexyl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide (0.50 g, 1.5 mmol) was stirred in 1:1 THF:MeOH (31 mL) at 0 °C and azetidine hydrochloride (0.72 g, 7.7 mmol) was added, followed by TEA (0.78 g, 7.7 mmol), acetic acid (0.93 g, 15 mmol), and sodium triacetoxyborohydride (0.98 g, 4.6 mmol). The resulting mixture was stirred at 0 °C for 30 minutes, then concentrated *in vacuo*, partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 0-15% MeOH/EtOAc with 3% NH_4OH). Desired fractions were identified, combined, and concentrated *in vacuo* to afford the title compound. LRMS (ESI) calc'd for $C_{20}H_{24}N_6O$ $[M+H]^+$: 365, Found: 365. ^1H NMR (500 MHz, DMSO-d_6): δ 9.15 (s, 1 H); 8.19 (s, 1 H); 7.66 (br s, 1 H); 7.49 (d, J = 8.1 Hz, 2 H); 7.24 (t, J = 7.7 Hz, 2 H); 7.14 (br s, 1 H); 6.82 (t, J = 7.3 Hz, 1 H); 4.39 (td, J = 11.2, 4.2 Hz, 1 H); 3.09 (t, J = 7.0 Hz, 4 H); 2.09-2.17 (m, 2 H); 1.84-1.98 (m, 5 H); 1.74-1.80 (m, 1 H); 1.36-1.38 (m, 1 H); 1.06-1.14 (m, 1 H).

Scheme #36 and 43

Example #28-5



1-((1R,2R,4R or 1S,2S,4S)-4-(*tert*-Butylamino)-2-cyanocyclohexyl)-3-((4-chlorophenyl)amino)-1*H*-pyrazole-4-carboxamide



Step A: **3-((4-Chlorophenyl)amino)-1-((1R,2R or 1S,2S)-2-cyano-4-oxocyclohexyl)-1*H*-pyrazole-4-carboxamide**

To a solution of 3-[(4-chlorophenyl)amino]-1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide **(Example 25-22)** (5.0 g, 14 mmol) in DMSO (99 mL) was added IBX (17.3 g, 27.8 mmol). The resulting mixture was heated to 50 °C for 2.5 hours, then cooled to ambient temperature and stirred with saturated aqueous sodium thiosulfate and saturated aqueous $NaHCO_3$ for 30 minutes. The mixture was extracted with EtOAc (3x). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 0-80% EtOAc/hexanes). Desired fractions were identified, combined, and concentrated *in vacuo* to afford the title compound. LRMS (ESI) calc'd for $C_{17}H_{16}ClN_5O_2$ $[M+H]^+$: 358, Found: 358.

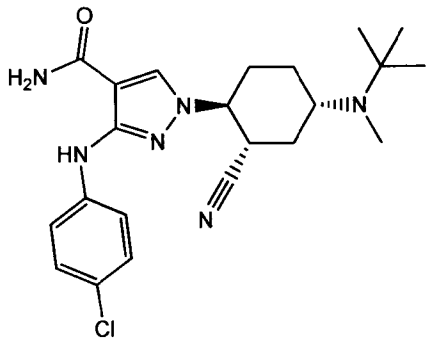
Step B: **1-((1R,2R,4R or 1S,2S,4S)-4-(*tert*-Butylamino)-2-cyanocyclohexyl)-3-((4-chlorophenyl)amino)-1*H*-pyrazole-4-carboxamide**

3-((4-Chlorophenyl)amino)-1-((1R,2R or 1S,2S)-2-cyano-4-oxocyclohexyl)-1*H*-pyrazole-4-carboxamide (100 mg, 0.28 mmol) was stirred in THF (2.8 mL) at ambient temperature and *tert*-butylamine (25 mg, 0.34 mmol), and titanium (IV) isopropoxide (175 mg, 0.62 mmol) was added. The resulting mixture was stirred at ambient temperature for 20 hours. MeOH (2.3 mL) was added and stirring continued for 30 minutes before sodium borohydride (11 mg, 0.28 mmol) was added. The resulting mixture was stirred at ambient temperature for 1 hour. The mixture was partitioned between EtOAc and 0.5 M aqueous NaOH. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (10% MeOH/EtOAc with 1% NH_4OH stepping to 2% NH_4OH after the first diastereomer elutes). Desired fractions were identified, combined, and concentrated *in vacuo* to afford the title compound. LRMS (ESI) calc'd for $C_{21}H_{27}ClN_6O$ $[M+H]^+$: 415, Found: 415. ^1H NMR (500 MHz, CD_3OD): δ 8.10 (s, 1 H); 7.53-7.54 (m, 2 H); 7.21-7.22 (m, 2 H); 4.23-4.24 (m, 1 H); 3.49-3.50 (m, 1 H); 2.84 (tt, J = 11.5, 3.9 Hz, 1 H); 2.34

(dd, J = 12.9, 3.6 Hz, 1 H); 2.18-2.20 (m, 1 H); 2.01 (s, 2 H); 1.67 (q, J = 12.3 Hz, 1 H); 1.43-1.45 (m, 1 H); 1.15 (s, 9 H).

Scheme #36 and 44

Example #28-6



1-((1S,2S,4S or 1R,2R,4R)-4-(tert-butyl(methyl)amino)-2-cyanocyclohexyl)-3-((4-chlorophenyl)amino)-1H-pyrazole-4-carboxamide

1-((1R,2R,4R or 1S,2S,4S)-4-(*tert*-Butylamino)-2-cyanocyclohexyl)-3-((4-chlorophenyl)amino)-1*H*-pyrazole-4-carboxamide **(Example 28-5)** (7.0 mg, 0.017 mmol) was stirred in 1:1 THF:MeOH (0.34 mL) at ambient temperature and sodium cyanoborohydride (1.6 mg, 0.025 mmol), acetic acid (0.0015 mL, 0.025 mmol), and aqueous formaldehyde (0.0019 mL, 0.025 mmol, 37% in water) were added. The resulting mixture was stirred at ambient temperature for 30 minutes, then concentrated *in vacuo* and partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title compound.

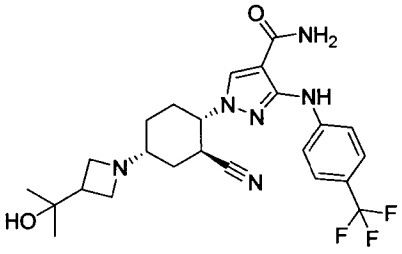
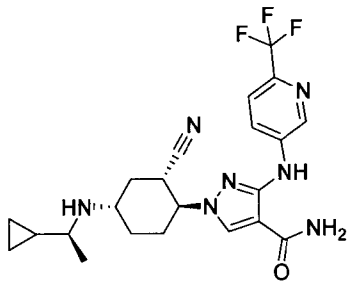
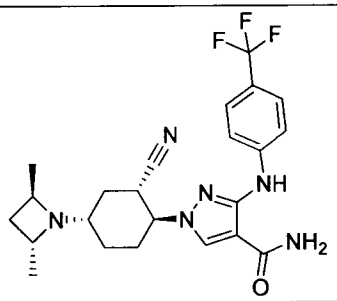
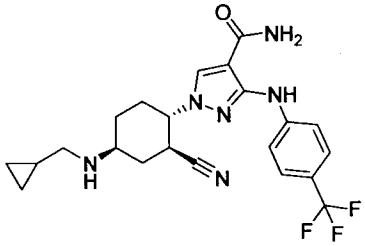
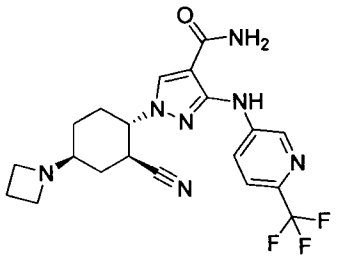
LRMS (ESI) calc'd for $C_{22}H_{30}ClN_6O$ $[M+H]^+$: 429, Found: 429.

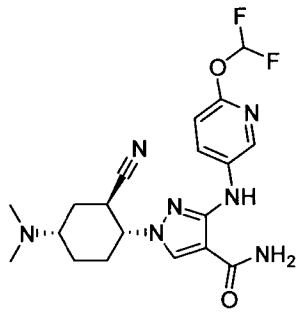
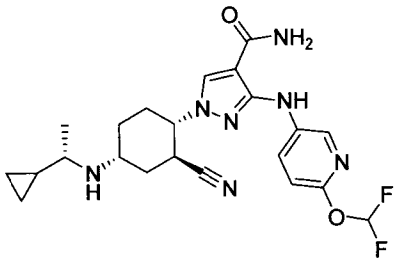
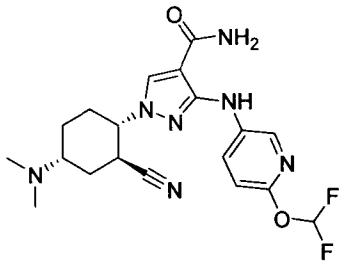
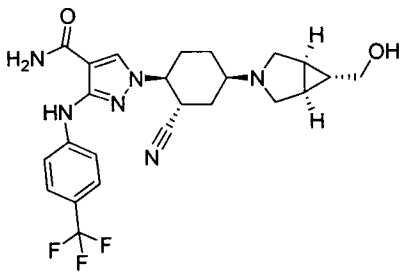
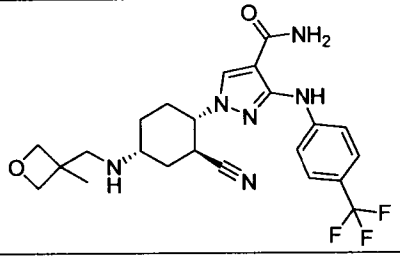
^1H NMR (500 MHz, CD_3OD): δ 8.10 (s, 1H), 7.54 (d, J = 9.0 Hz, 2H) 7.23 (d, J = 9.0 Hz, 2H), 4.22 (td, J = 11.5, 4.3 Hz, 1H), 3.52 (td, J = 12.5, 3.5 Hz, 1H), 3.16-3.12 (m, 1H), 2.29 (s, 3H), 2.20-2.05 (m, 3H), 2.00-1.82 (m, 2H), 1.74 (qd, J = 12.7, 3.7 Hz, 1H), 1.17 (s, 9H).

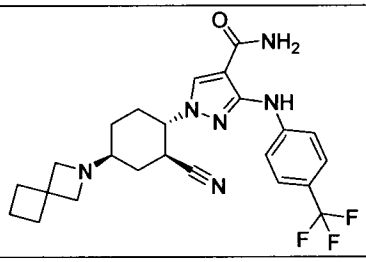
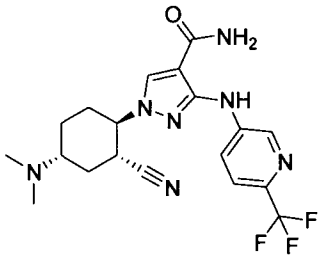
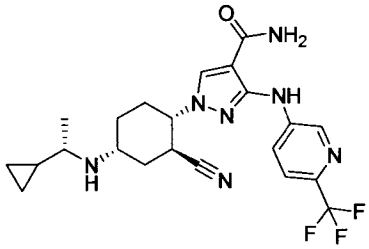
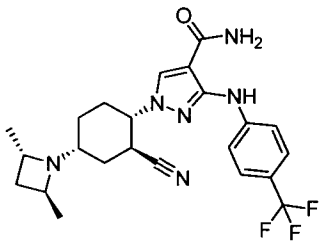
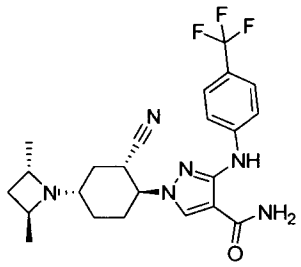
The following compounds shown in **TABLE 23** were prepared according to **Scheme #36 and 40, 41, 42, 43, and 44** following similar procedures described for **Examples #28-1, 28-2, 28-3, 28-4, 28-5, and 28-6**, which can be achieved by those of ordinary skill in the art of organic synthesis. As an alternative to using chiral stationary phase chromatography, according to **Scheme #36**, chiral alcohol **Intermediate #40** could be utilized thus providing chiral intermediate ketones, and non-racemic diastereomeric reductive amination products.

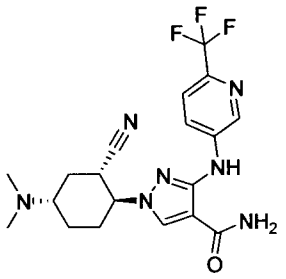
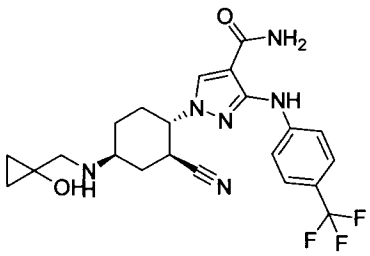
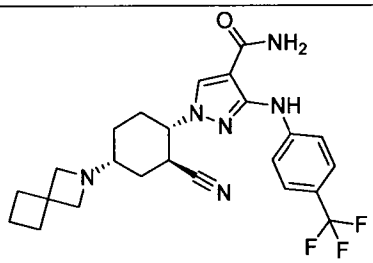
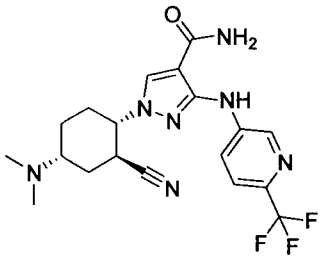
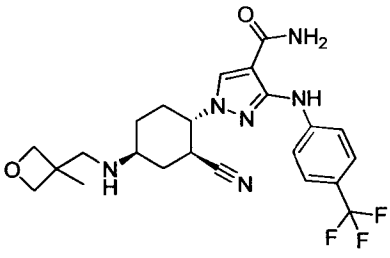
TABLE 23:

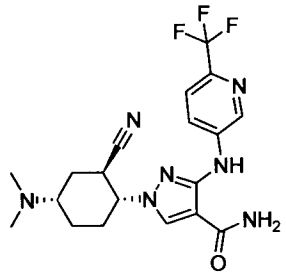
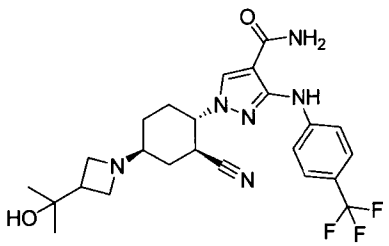
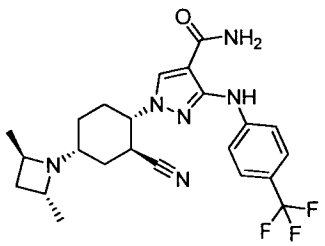
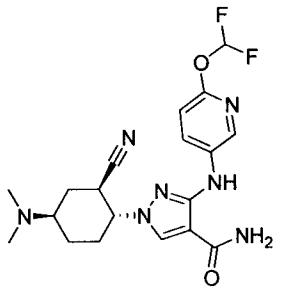
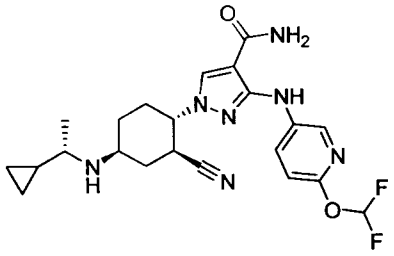
Example	Method	Structure	Compound Name	Exact Mass [M+H]+

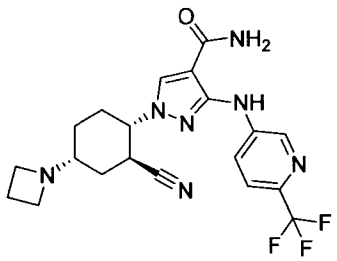
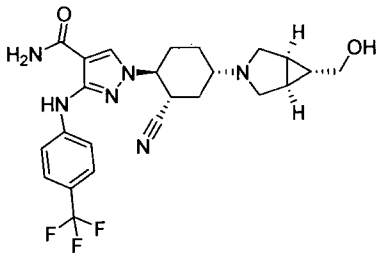
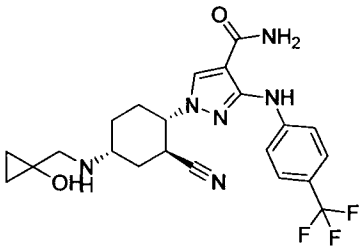
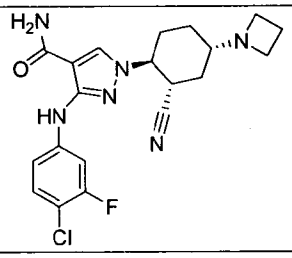
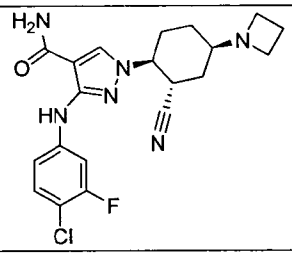
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-7	40		1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[3-(1-hydroxy-1-methylethyl)azetidin-1-yl]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 491, found 491
28-8	40		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(1S)-1-cyclopropylethyl]amino}cyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 462, found 462
28-9	40		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2R,4R or 2S,4S)-2,4-dimethylazetidin-1-yl]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 461, found 461
28-10	40		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(cyclopropylmethyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 447, found 447
28-11	41		1-[(1S,2S,4S or 1R,2R,4R)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 434, found 434

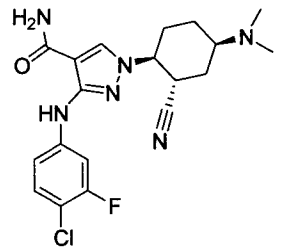
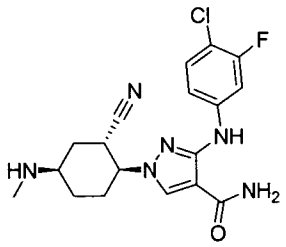
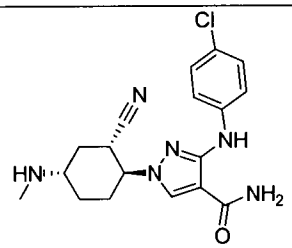
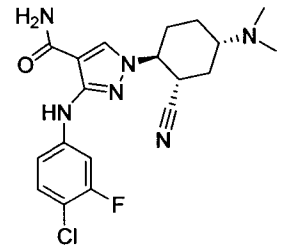
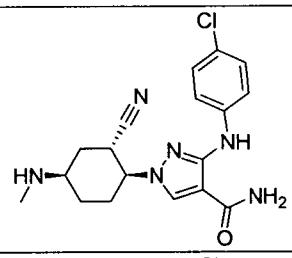
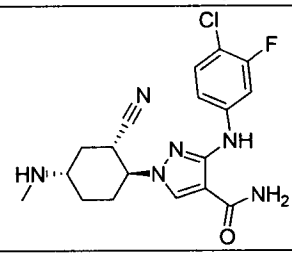
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-12	41		1-[(1R,2R,4S or 1S,2S,4R)-2-cyano-4-(dimethylamino)cyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 420, found 420
28-13	41		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-{[(1S)-1-cyclopropylethyl]amino}cyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 460, found 460
28-14	41		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(dimethylamino)cyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 420, found 420
28-15	40		1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[(1R,5S,6R or 1S,5R,6S)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hex-3-yl]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 489, found 489
28-16	40		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-{[(3-methyloxetan-3-yl)methyl]amino}cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino	Calc'd 477, found 477

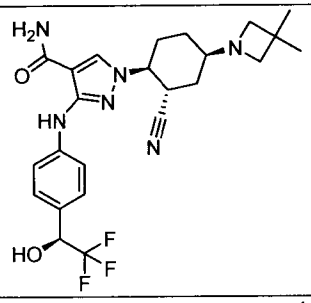
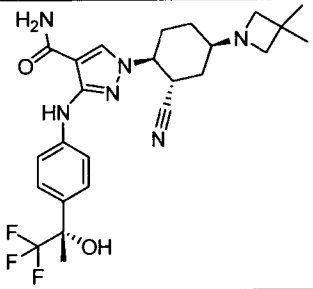
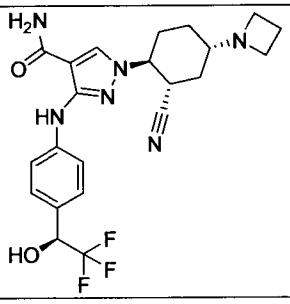
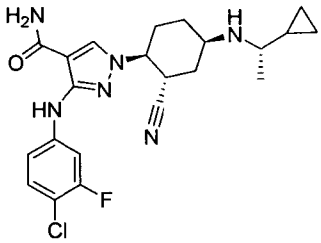
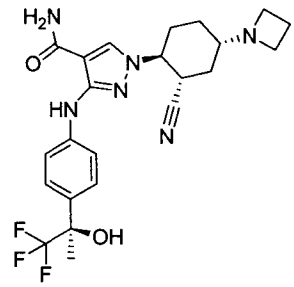
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
			}-1*H*-pyrazole-4-carboxamide	
28-17	**40**		1-[(1S,2S,4S or 1R,2R,4R)-4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 473, found 473
28-18	**41**		1-[(1R,2R,4R or 1S,2S,4S)-2-cyano-4-(dimethylamino)cyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 422, found 422
28-19	**41**		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-{[(1S)-1-cyclopropylethyl]amino}cyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 462, found 462
28-20	**40**		1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[(2S,4S or 2R,4R)-2,4-dimethylazetidin-1-yl]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 461, found 461
28-21	**40**		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2S,4S or 2R,4R)-2,4-dimethylazetidin-1-yl]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 461, found 461

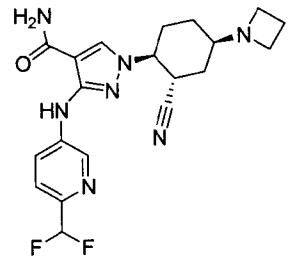
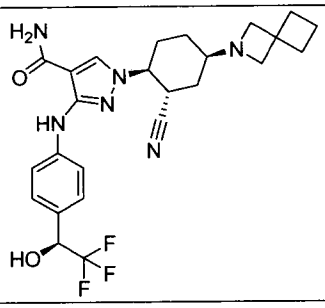
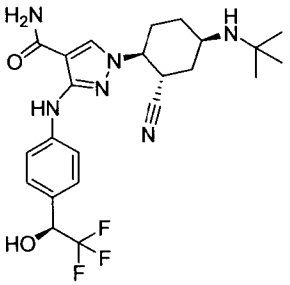
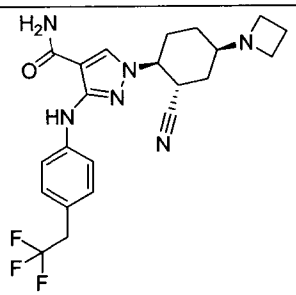
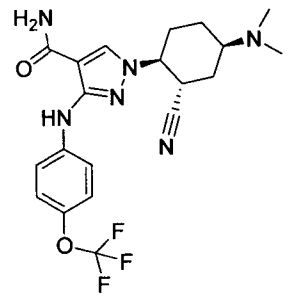
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-22	41		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(dimethylamino)cyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 422, found 422
28-23	40		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(1-hydroxycyclopropyl)methyl]amino}cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 463, found 463
28-24	40		1-[(1S,2S,4R or 1R,2R,4S)-4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 473, found 473
28-25	41		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(dimethylamino)cyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 422, found 422
28-26	40		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(3-methyloxetan-3-yl)methyl]amino}cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 477, found 477

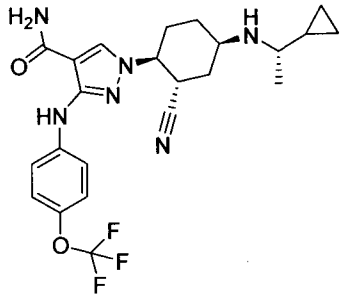
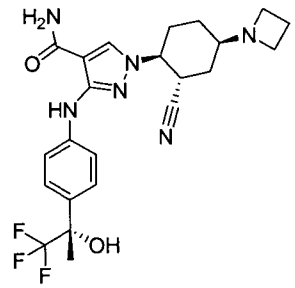
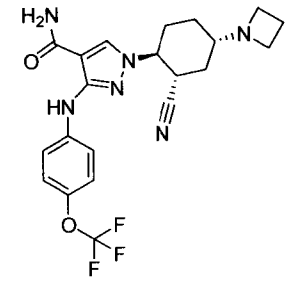
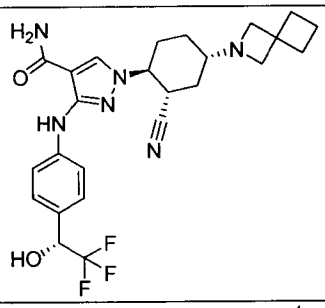
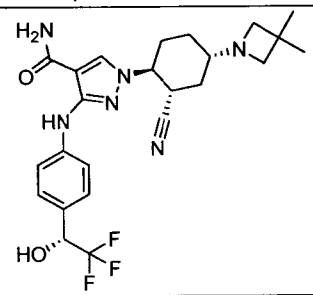
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-27	41		1-[(1R,2R,4S or 1S,2S,4R)-2-cyano-4-(dimethylamino)cyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 422, found 422
28-28	40		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[3-(1-hydroxy-1-methylethyl)azetidin-1-yl]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 491, found 491
28-30	40		1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[(2R,4R or 2S,4S)-2,4-dimethylazetidin-1-yl]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 461, found 461
28-31	41		1-[(1R,2R,4R pr 1S,2S,4S)-2-cyano-4-(dimethylamino)cyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 420, found 420
28-32	41		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(1S)-1-cyclopropylethyl]amino}cyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 460, found 460

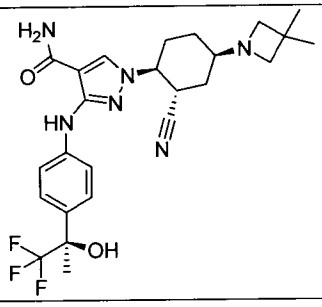
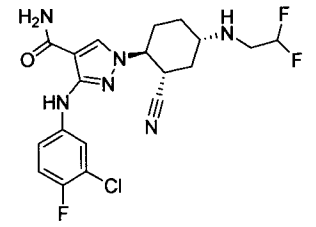
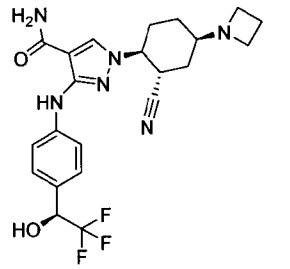
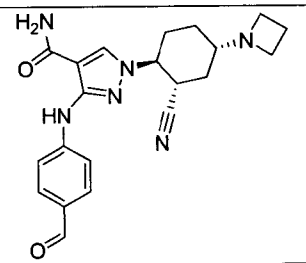
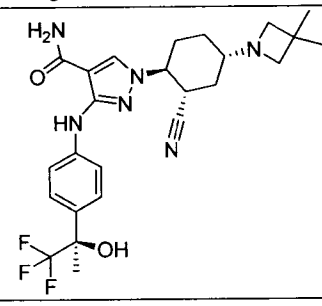
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-33	41		1-[(1S,2S,4R or 1R,2R,4S)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 434, found 434
28-34	40		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(1R,5S,6S or 1S,5R,6R)-6-(hydroxymethyl)-3-azabicyclo[3.1.0]hex-3-yl]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 489, found 489
28-35	40		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-{[(1-hydroxycyclopropyl)methyl]amino}cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 463, found 463
28-36	40		1-[(1S,2S,4S or 1R,2R,4R)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(4-chloro-3-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 417, found 417
28-37	40		1-[(1S,2S,4R or 1R,2R,4S)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(4-chloro-3-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 417, found 417

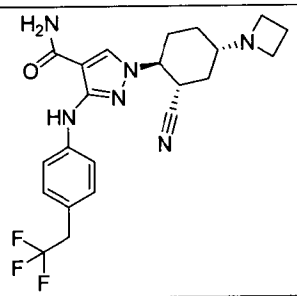
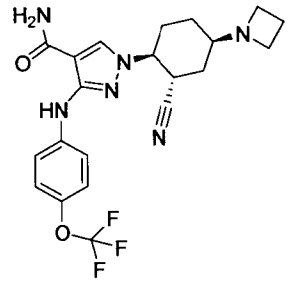
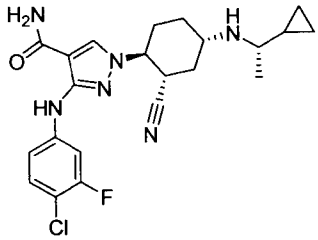
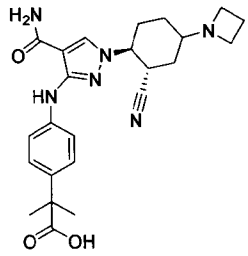
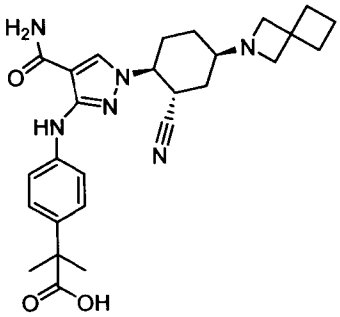
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-38	40		3-[(4-chloro-3-fluorophenyl)amino]-1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(dimethylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 405, found 405
28-39	40		3-[(4-chloro-3-fluorophenyl)amino]-1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(methylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 391, found 391
28-40	41		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(methylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 373, found 373
28-41	40		3-[(4-chloro-3-fluorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(dimethylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 405, found 405
28-42	41		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(methylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 373, found 373
28-43	40		3-[(4-chloro-3-fluorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(methylamino)cyclohexyl]-	Calc'd 391, found 391

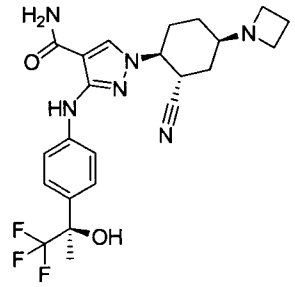
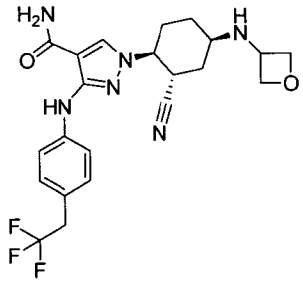
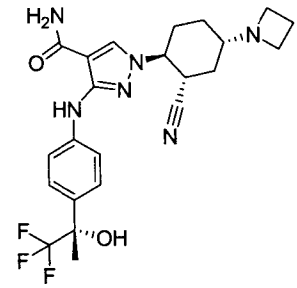
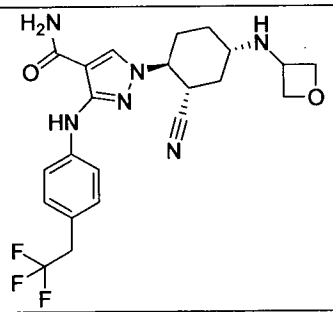
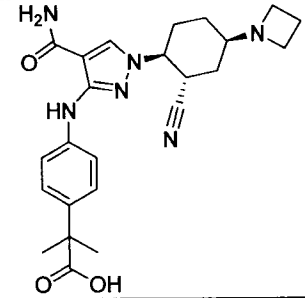
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
			1*H*-pyrazole-4-carboxamide	
28-44	**40**		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 491, found 491
28-45	**40**		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 505, found 505
28-47	**40**		1-[(1S,2S,4S or 1R,2R,4R)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 463, found 463
28-48	**40**		3-[(4-chloro-3-fluorophenyl)amino]-1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-{[(1S or 1R)-1-cyclopropylethyl]amino}cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 445, found 445
28-49	**40**		1-[(1S,2S,4S or 1R,2R,4R)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 477, found 477

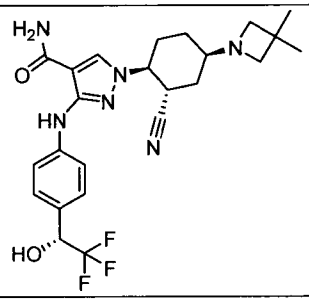
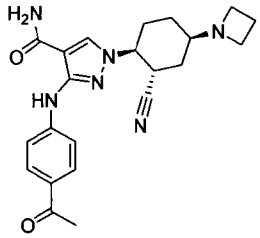
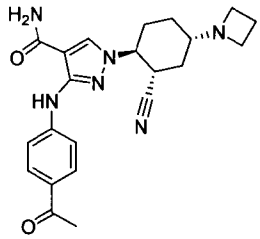
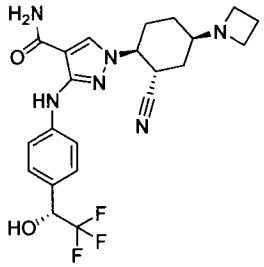
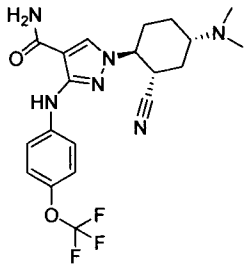
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-50	40		1-[(1S,2S,4R or 1R,2R,4S)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[6-(difluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 416, found 416
28-51	40		1-[(1S,2S,4R or 1R,2R,4S)-4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 503, found 503
28-52	40		1-[(1S,2S,4R or 1R,2R,4S)-4-(tert-butylamino)-2-cyanocyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 479, found 479
28-53	40		1-[(1S,2S,4R or 1R,2R,4S)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[4-(2,2,2-trifluoroethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 447, found 447
28-54	40		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(dimethylamino)cyclohexyl]-3-{[4-(trifluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 437, found 437

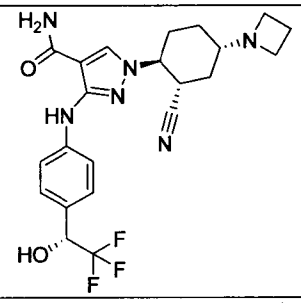
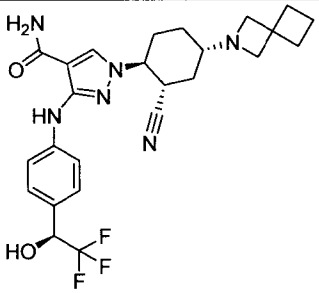
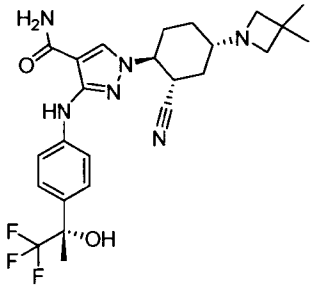
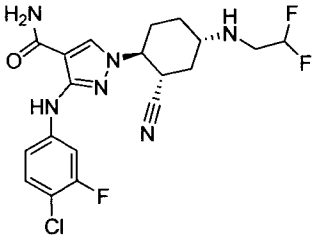
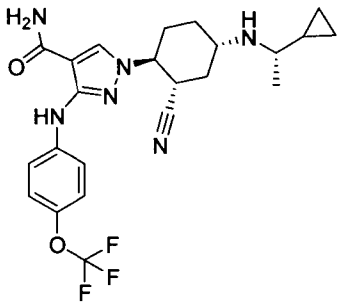
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-55	40		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-{[(1S)-1-cyclopropylethyl]amino}cyclohexyl]-3-{[4-(trifluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 477, found 477
28-57	40		1-[(1S,2S,4R or 1R,2R,4S)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 477, found 477
28-58	40		1-[(1S,2S,4S or 1R,2R,4R)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[4-(trifluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 449, found 449
28-60	40		1-[(1S,2S,4S or 1R,2R,4R)-4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 503, found 503
28-61	40		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 491, found 491

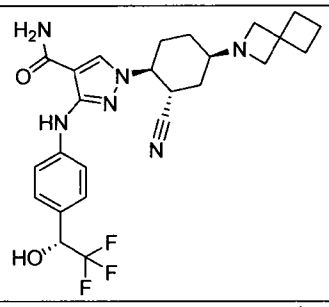
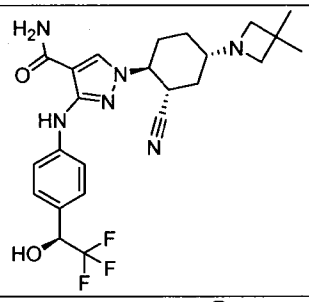
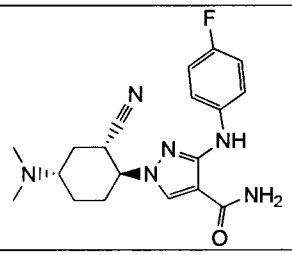
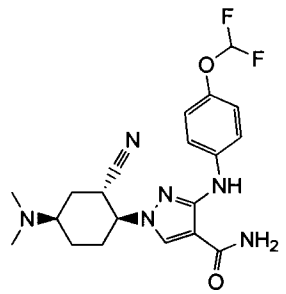
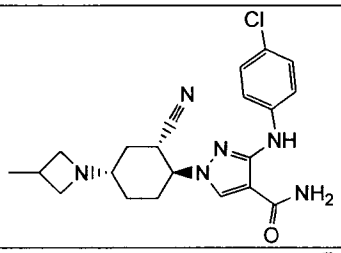
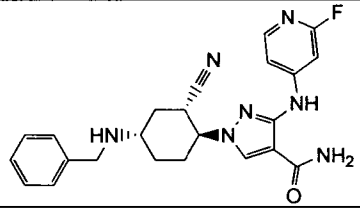
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-62	40		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 505, found 505
28-63	40		3-[(3-chloro-4-fluorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 441, found 441
28-65	40		1-[(1S,2S,4R or 1R,2R,4S)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 463, found 463
28-66	40		1-[(1S,2S,4S or 1R,2R,4R)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(4-formylphenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 393, found 393
28-68	40		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 505, found 505

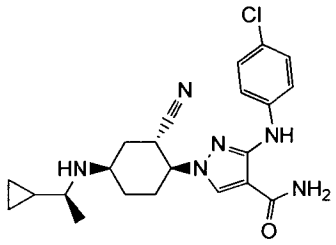
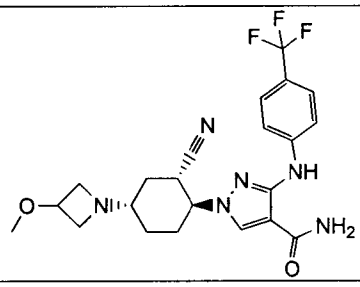
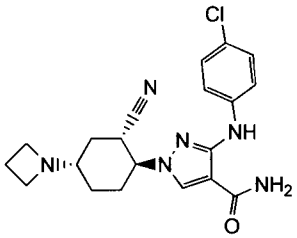
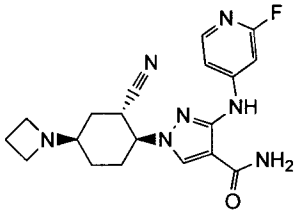
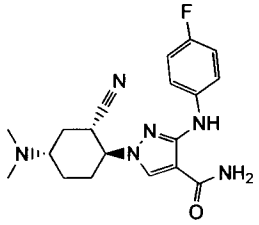
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-69	40		1-[(1S,2S,4S or 1R,2R,4R)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[4-(2,2,2-trifluoroethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 447, found 447
28-70	40		1-[(1S,2S,4R or 1R,2R,4S)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[4-(trifluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 449, found 449
28-71	40		3-[(4-chloro-3-fluorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(1S or 1R)-1-cyclopropylethyl]amino}cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 445, found 445
28-72	40		2-[4-({1-[(1S,2S or 1R,2R)-4-azetidin-1-yl-2-cyanocyclohexyl]-4-carbamoyl-1*H*-pyrazol-3-yl}amino)phenyl]-2-methylpropanoic acid	Calc'd 451, found 451
28-75	40		2-[4-({1-[(1S,2S,4R or 1R,2R,4S)-4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-4-carbamoyl-1*H*-pyrazol-3-yl}amino)phenyl]-2-methylpropanoic acid	Calc'd 491, found 491

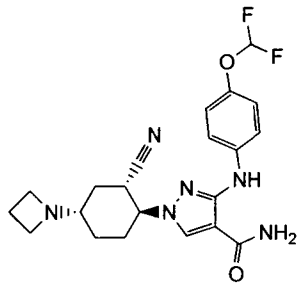
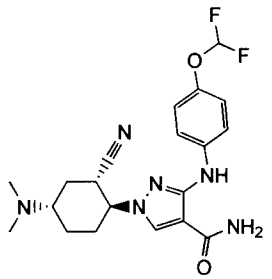
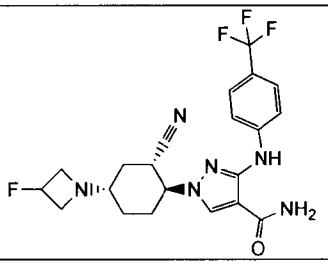
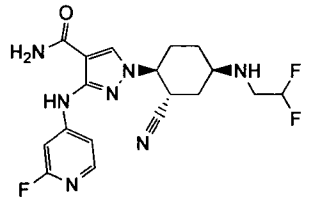
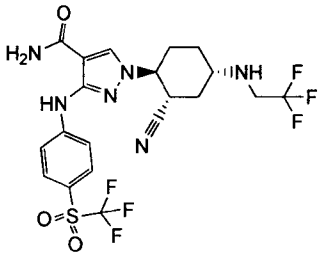
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-76	40		1-[(1S,2S,4R or 1R,2R,4S)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 477, found 477
28-77	40		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(oxetan-3-ylamino)cyclohexyl]-3-{[4-(2,2,2-trifluoroethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 463, found 463
28-78	40		1-[(1S,2S,4S or 1R,2R,4R)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 477, found 477
28-79	40		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(oxetan-3-ylamino)cyclohexyl]-3-{[4-(2,2,2-trifluoroethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 463, found 463
28-80	40		2-[4-({1-[(1S,2S,4R or 1R,2R,4S)-4-azetidin-1-yl-2-cyanocyclohexyl]-4-carbamoyl-1*H*-pyrazol-3-yl}amino)phenyl]-2-methylpropanoic acid	Calc'd 451, found 451

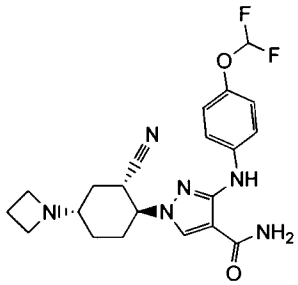
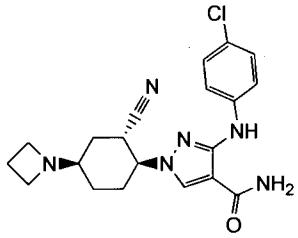
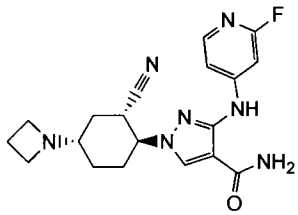
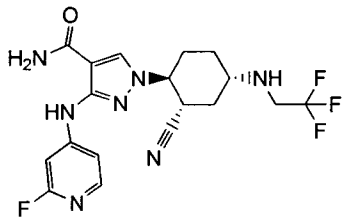
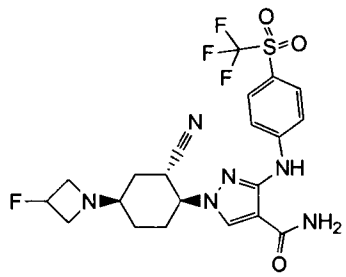
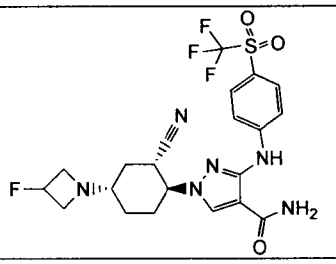
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-81	40		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 491, found 491
28-83	40		3-[(4-acetylphenyl)amino]-1-[(1S,2S,4R or 1R,2R,4S)-4-azetidin-1-yl-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 407, found 407
28-84	40		3-[(4-acetylphenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-4-azetidin-1-yl-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 407, found 407
28-85	40		1-[(1S,2S,4R or 1R,2R,4S)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 463, found 463
28-86	40		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(dimethylamino)cyclohexyl]-3-{[4-(trifluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 437, found 437

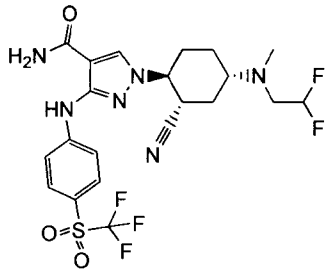
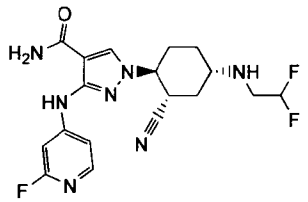
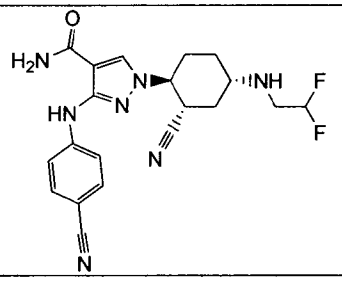
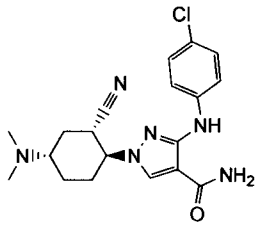
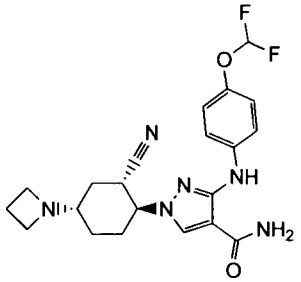
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-87	40		1-[(1S,2S,4S or 1R,2R,4R)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 463, found 463
28-88	40		1-[(1S,2S,4S or 1R,2R,4R)-4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 503, found 503
28-89	40		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 505, found 505
28-90	40		3-[(4-chloro-3-fluorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 441, found 441
28-91	40		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(1S)-1-cyclopropylethyl]amino}cyclohexyl]-3-{[4-(trifluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 477, found 477

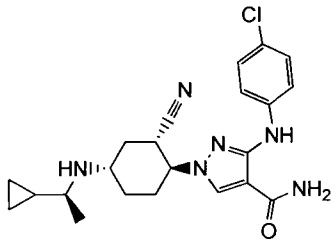
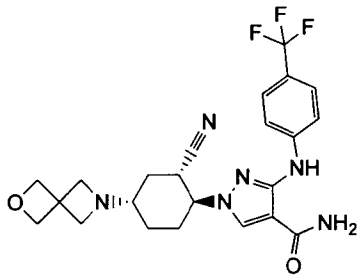
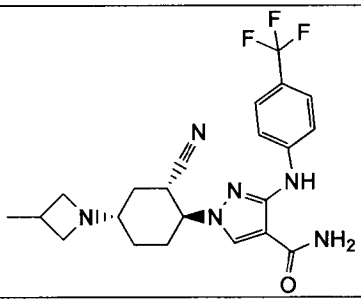
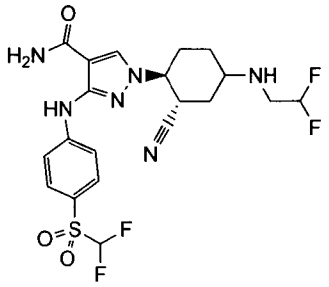
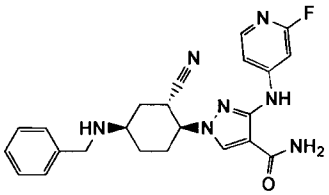
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-92	**40**		1-[(1S,2S,4R or 1R,2R,4S)-4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 503, found 503
28-93	**40**		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 491, found 491
28-94	**40**		1-[(1S,2S,4S or 1R,2R,4S)-2-cyano-4-(dimethylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 371, found 371
28-95	**40**		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(dimethylamino)cyclohexyl]-3-{[4-(difluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 419, found 419
28-96	**41**		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3-methylazetidin-1-yl)cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 413, found 413
28-97	**40**		1-[(1S,2S,4S or 1R,2R,4R)-4-(benzylamino)-2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-	Calc'd 434, found 434

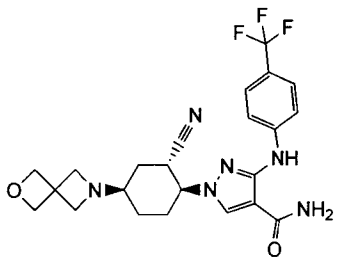
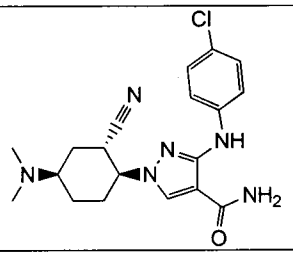
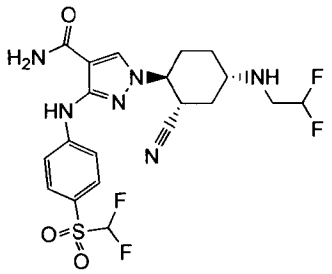
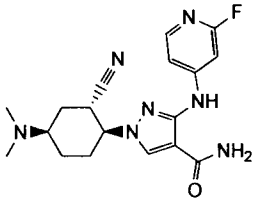
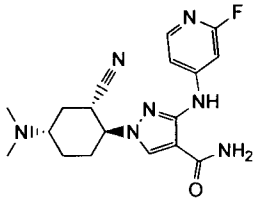
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
			pyrazole-4-carboxamide	
28-98	**41**		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-{[(1S)-1-cyclopropylethyl]amino}cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 427, found 427
28-99	**41**		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3-methoxyazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 463, found 463
28-100	**41**		1-[(1S,2S,4S or 1R,2R,4R)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(4-chlorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 399, found 399
28-101	**41**		1-[(1S,2S,4R or 1R,2R,4S)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 384, found 384
28-102	**40**		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(dimethylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 371, found 371

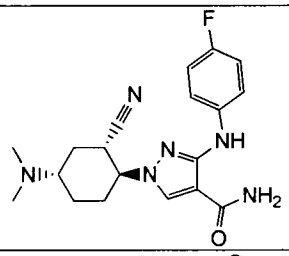
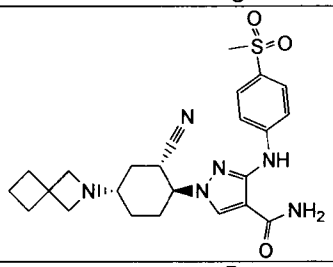
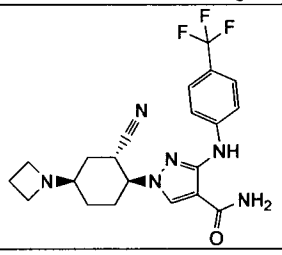
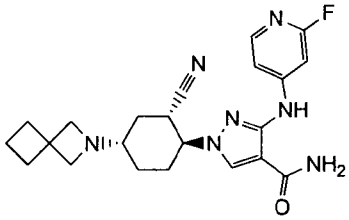
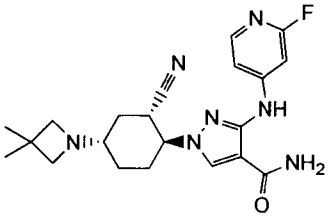
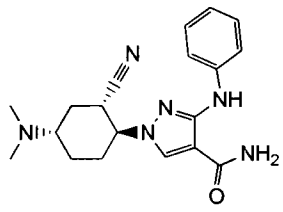
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-103	40		1-[(1S,2S,4S or 1R,2R,4R)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[4-(difluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 431, found 431
28-104	40		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(dimethylamino)cyclohexyl]-3-{[4-(difluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 419, found 419
28-105	41		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3-fluoroazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 451, found 451
28-106	40		1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 408, found 408
28-107	40		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2,2,2-trifluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 539, found 539

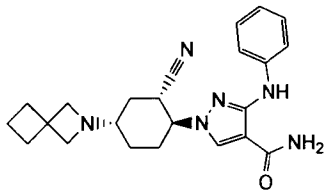
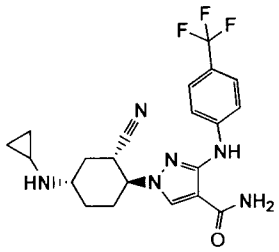
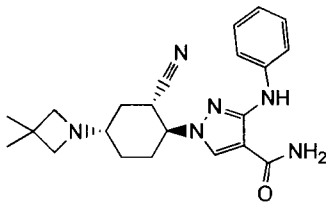
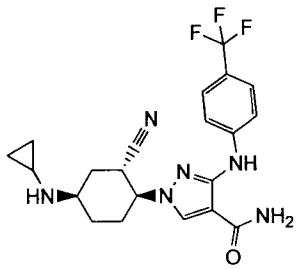
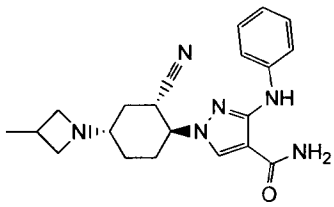
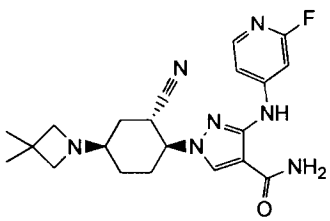
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-108	40		1-[(1S,2S,4S or 1R,2R,4R)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[4-(difluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 431, found 431
28-109	41		1-[(1S,2S,4R or 1R,2R,4S)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(4-chlorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 399, found 399
28-110	41		1-[(1S,2S,4S or 11R,2R,4R)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 384, found 384
28-111	41		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2,2,2-trifluoroethyl)amino]cyclohexyl}-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 426, found 426
28-112	40		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(3-fluoroazetidin-1-yl)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 515, found 515
28-113	40		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3-fluoroazetidin-1-yl)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-	Calc'd 515, found 515

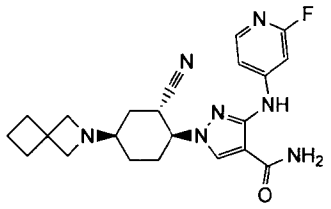
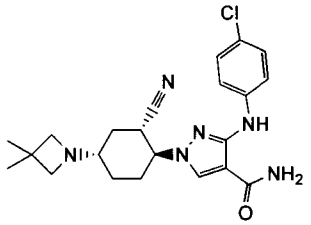
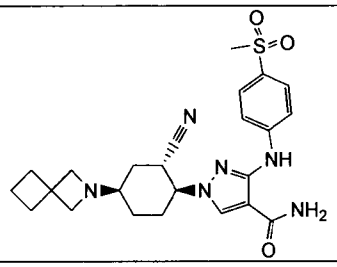
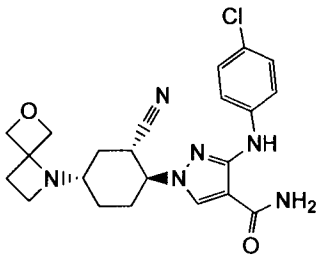
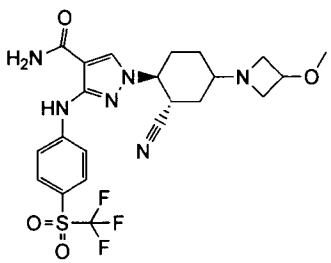
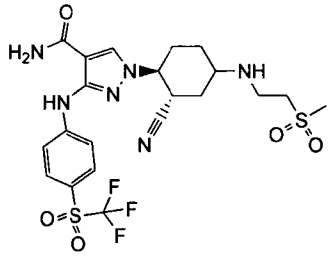
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
			carboxamide	
28-114	**40**		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2,2-difluoroethyl)(methyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 535, found 535
28-115	**40**		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 408, found 408
28-116	**40**		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-3-[(4-cyanophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 414, found 414
28-117	**41**		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(dimethylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 387, found 387
28-118	**40**		1-[(1S,2S,4S or 1R,2R,4R)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[4-(difluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 431, found 431

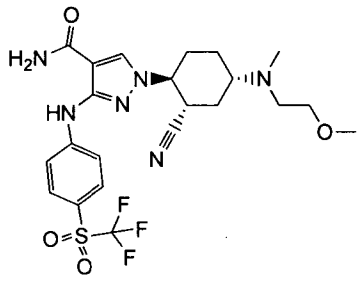
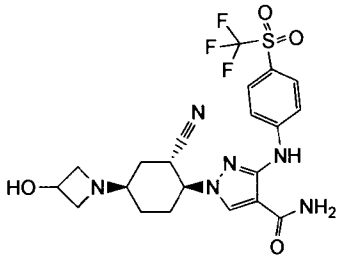
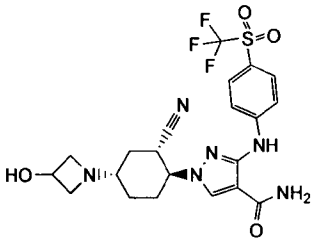
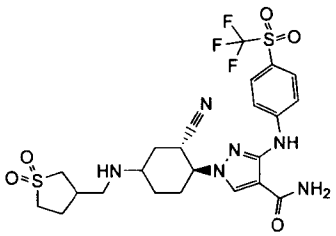
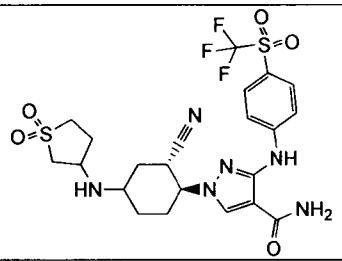
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-119	41		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(1R)-1-cyclopropylethyl]amino}cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 427, found 427
28-120	41		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(2-oxa-6-azaspiro[3.3]hept-6-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 475, found 475
28-121	41		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3-methylazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 447, found 447
28-122	40		1-{(1S,2S or 1R,2R)-2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-3-({4-[(difluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 503, found 503
28-123	40		1-[(1S,2S,4R or 1R,2R,4S)-4-(benzylamino)-2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 434, found 434

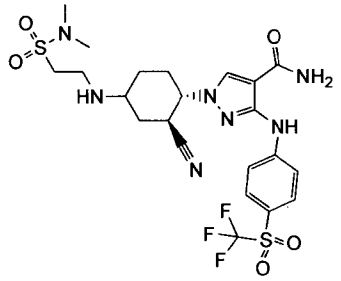
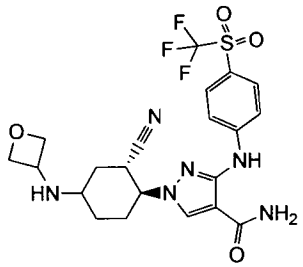
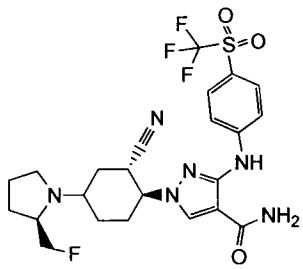
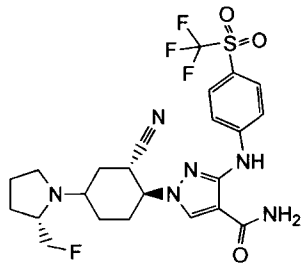
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-124	41		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(2-oxa-6-azaspiro[3.3]hept-6-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 475, found 475
28-125	41		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(dimethylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 387, found 387
28-126	40		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-3-({4-[(difluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 503, found 503
28-127	40		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(dimethylamino)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 372, found 372
28-128	40		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(dimethylamino)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 372, found 372

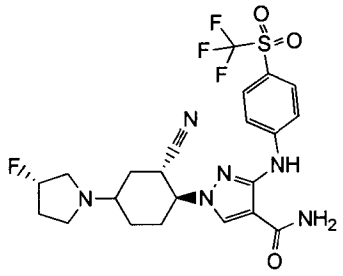
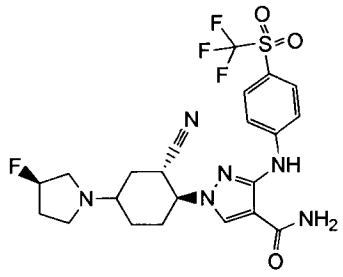
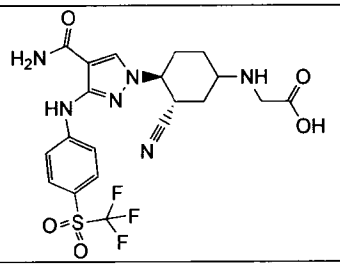
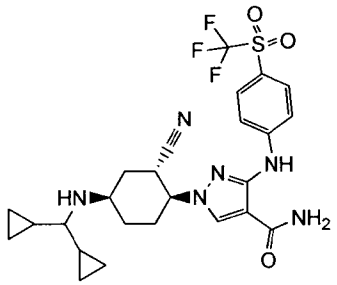
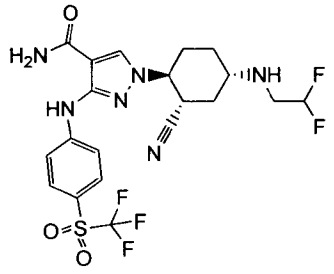
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-129	40		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(dimethylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 371, found 371
28-130	41		1-[(1S,2S,4S or 1R,2R,4R)-4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 483, found 483
28-131	41		1-[(1S,2S,4R or 1R,2R,4S)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 433, found 433
28-133	41		1-[(1S,2S,4S or 1R,2R,4R)-4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 424, found 424
28-134	41		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 412, found 412
28-135	42		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(dimethylamino)cyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 353, found 353

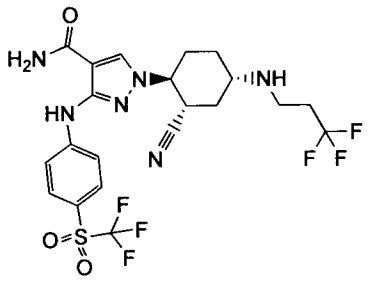
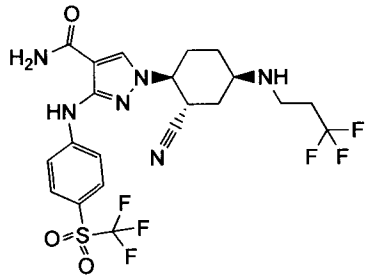
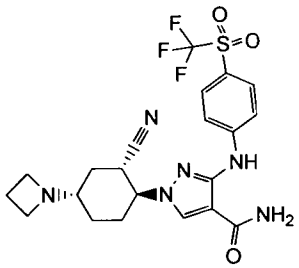
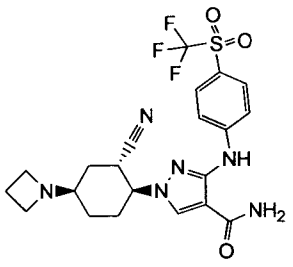
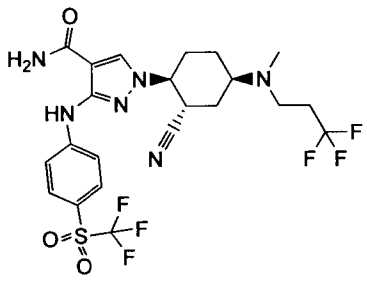
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-136	42		1-[(1S,2S,4S or 1R,2R,4R)-4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 405, found 405
28-137	41		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(cyclopropylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 433, found 433
28-138	41		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 393, found 393
28-139	41		1-[(1S,2S,4R or 1R,2R,4R)-2-cyano-4-(cyclopropylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 433, found 433
28-141	41		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3-methylazetidin-1-yl)cyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide	Calc'd 379, found 379
28-142	41		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 412, found 412

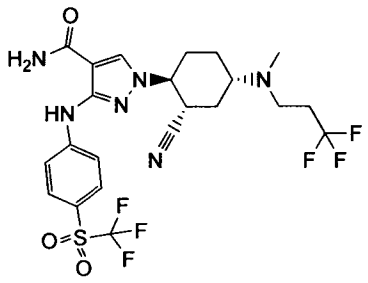
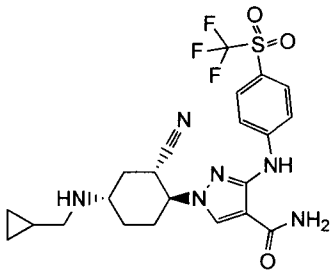
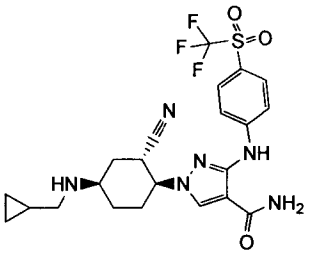
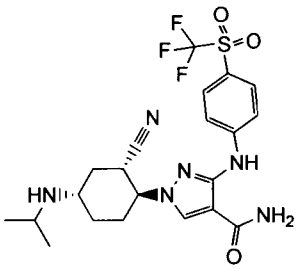
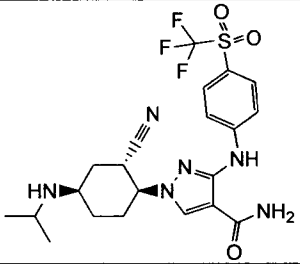
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-143	41		1-[(1S,2S,4R or 1R,2R,4S)-4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 424, found 424
28-144	41		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 427, found 427
28-145	41		1-[(1S,2S,4R or 1R,2R,4S)-4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 483, found 483
28-146	41		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(6-oxa-1-azaspiro[3.3]hept-1-yl)cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 441, found 441
28-147	40		1-[(1S,2S or 1R,2R)-2-cyano-4-(3-methoxyazetidin-1-yl)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 527, found 527
28-148	40		1-[(1S,2S or 1R,2R)-2-cyano-4-{[2-(methylsulfonyl)ethyl]amino}cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-	Calc'd 563, found 563

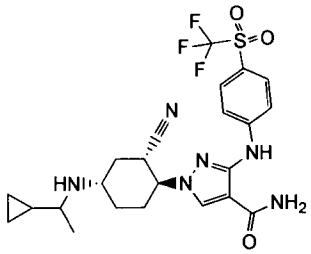
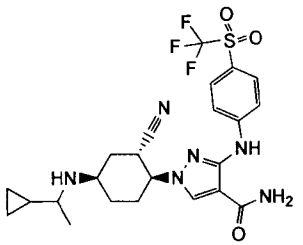
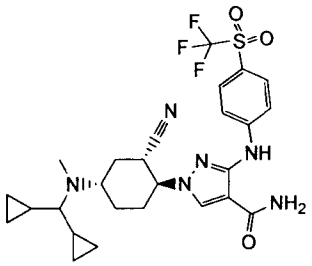
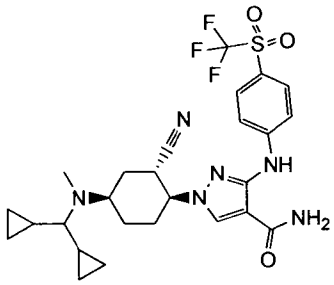
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
			carboxamide	
28-149	40		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2-methoxyethyl)(methyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 529, found 529
28-150	40		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(3-hydroxyazetidin-1-yl)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 513, found 513
28-151	40		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3-hydroxyazetidin-1-yl)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 513, found 513
28-152	40		1-[(1S,2S or 1R,2R)-2-cyano-4-{[(1,1-dioxidotetrahydrothiophen-3-yl)methyl]amino}cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 589, found 589
28-153	40		1-{(1S,2S or 1R,2R)-2-cyano-4-[(1,1-dioxidotetrahydrothiophen-3-yl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phe	Calc'd 575, found 575

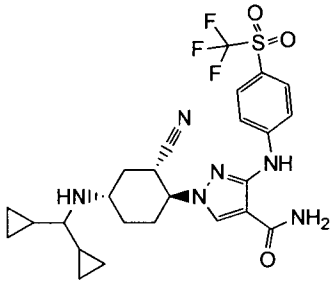
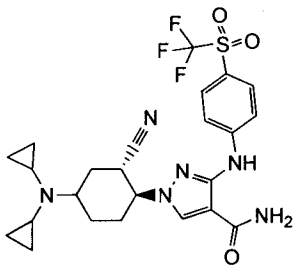
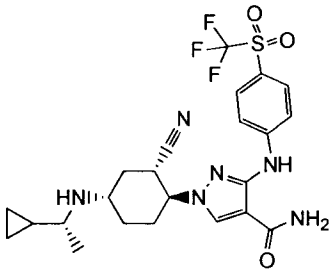
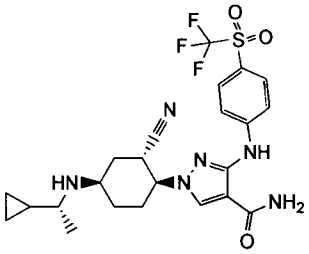
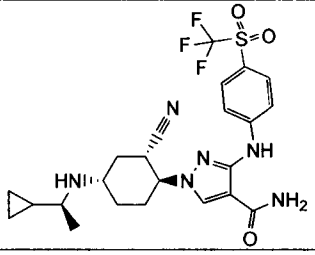
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
			nyl}amino)-1*H*-pyrazole-4-carboxamide	
28-154	**40**		1-[(1S,2S or 1R,2R)-2-cyano-4-{[2-(dimethylsulfamoyl)ethyl]amino}cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 592, found 592
28-155	**40**		1-[(1S,2S or 1R,2R)-2-cyano-4-(oxetan-3-ylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 513, found 513
28-156	**40**		1-{(1S,2S or 1R,2R)-2-cyano-4-[(2R)-2-(fluoromethyl)pyrrolidin-1-yl]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 543, found 543
28-157	**40**		1-{(1S,2S or 1R,2R)-2-cyano-4-[(2S)-2-(fluoromethyl)pyrrolidin-1-yl]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 543, found 543

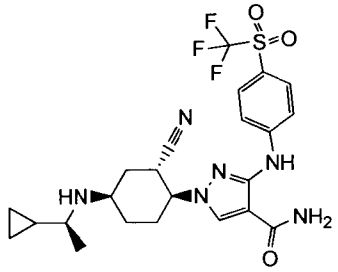
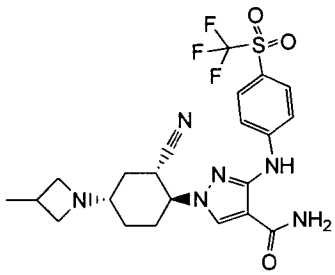
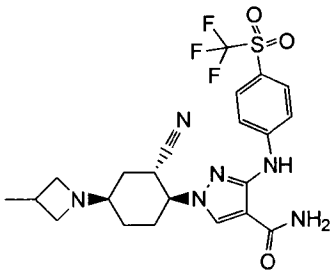
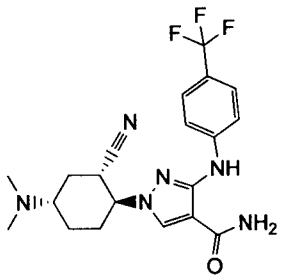
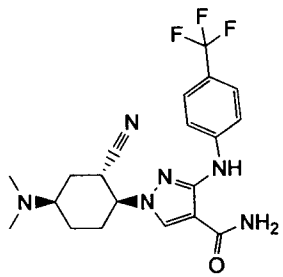
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-158	40		1-{(1S,2S or 1R,2R)-2-cyano-4-[(3S)-3-fluoropyrrolidin-1-yl]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 529, found 529
28-159	40		1-{(1S,2S or 1R,2R)-2-cyano-4-[(3R)-3-fluoropyrrolidin-1-yl]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 529, found 529
28-160	40		N-{(3S,4S or 3R,4R)-4-[4-carbamoyl-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazol-1-yl]-3-cyanocyclohexyl}glycine	Calc'd 515, found 515
28-164	40		1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[(dicyclopropylmethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 551, found 551
28-165	40		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 521, found 521

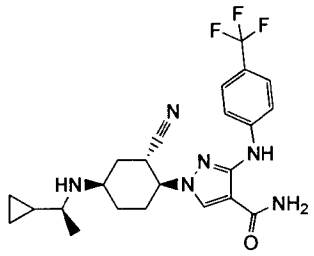
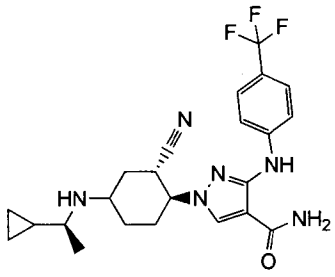
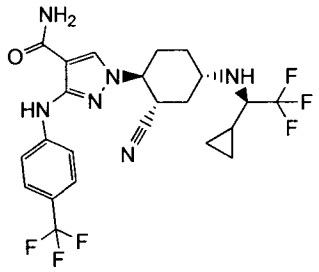
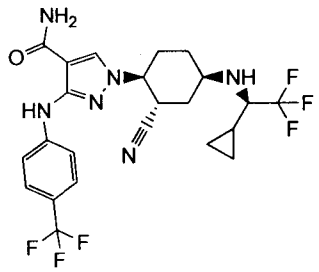
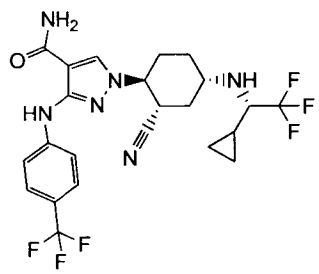
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-166	40		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(3,3,3-trifluoropropyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 553, found 553
28-167	40		1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[(3,3,3-trifluoropropyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 553, found 553
28-168	40		1-[(1S,2S,4S or 1R,2R,4R)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 497, found 497
28-169	40		1-[(1S,2S,4R or 1R,2R,4S)-4-azetidin-1-yl-2-cyanocyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 497, found 497
28-170	40		1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[methyl(3,3,3-trifluoropropyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 567, found 567

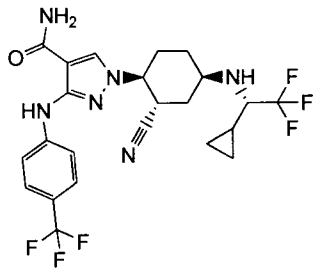
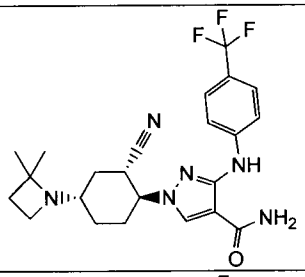
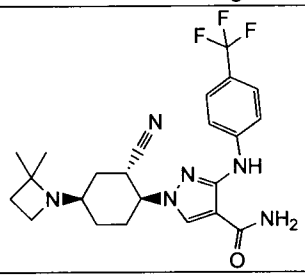
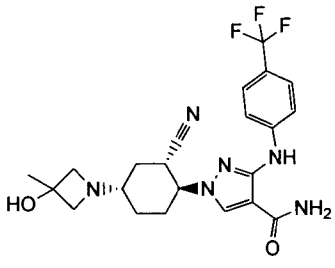
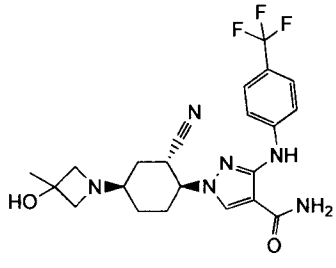
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-171	40		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[methyl(3,3,3-trifluoropropyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 567, found 567
28-172	40		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(cyclopropylmethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 511, found 511
28-173	40		1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[(cyclopropylmethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 511, found 511
28-174	40		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(1-methylethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 499, found 499
28-175	40		1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[(1-methylethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phe	Calc'd 499, found 499

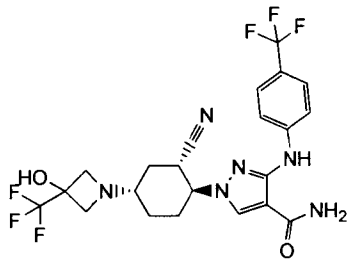
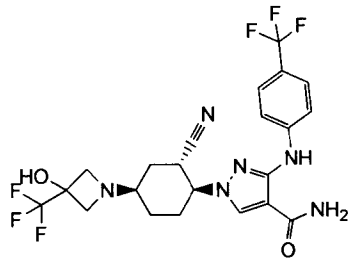
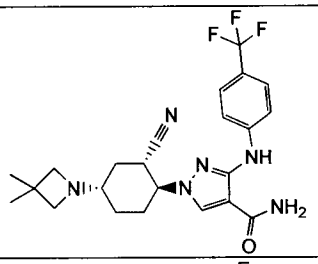
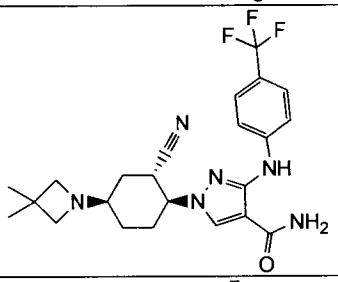
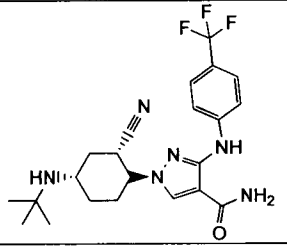
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
			nyl}amino)-1*H*-pyrazole-4-carboxamide	
28-176	**40**		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(1R)-1-cyclopropylethyl]amino}cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 525, found 525
28-177	**40**		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-{[(1S)-1-cyclopropylethyl]amino}cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 525, found 525
28-178	**40**		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(dicyclopropylmethyl)(methyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 565, found 565
28-179	**40**		1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[(dicyclopropylmethyl)(methyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 565, found 565

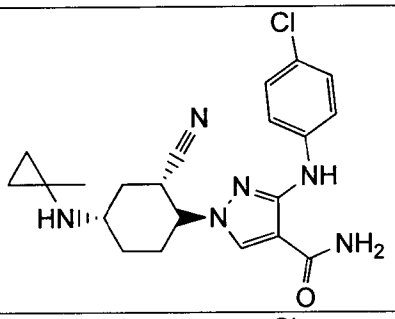
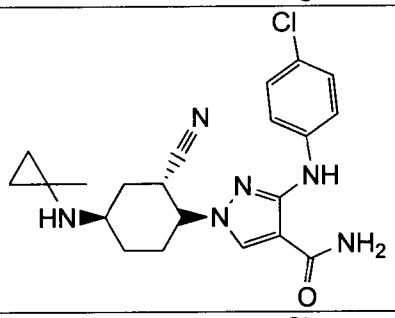
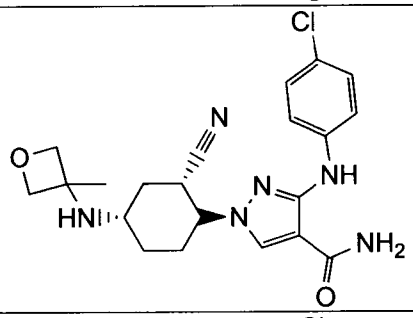
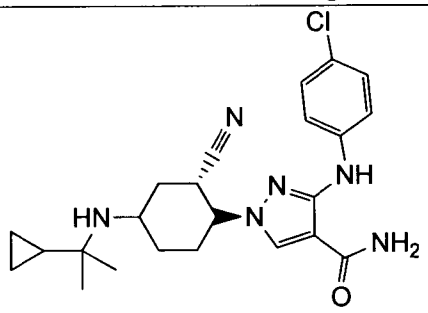
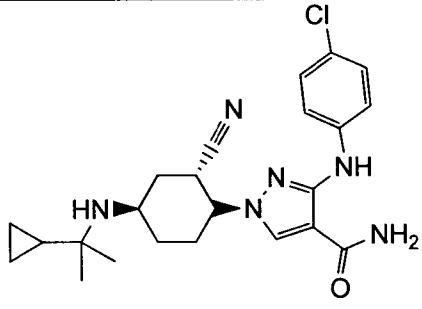
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-180	40		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(dicyclopropylmethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 551, found 551
28-181	40		1-[(1S,2S or 1R,2R)-2-cyano-4-(dicyclopropylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 537, found 537
28-182	40		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(1R)-1-cyclopropylethyl]amino}cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 525, found 525
28-183	40		1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[(1-cyclopropylethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 525, found 525
28-184	40		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(1-cyclopropylethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phe	Calc'd 525, found 525

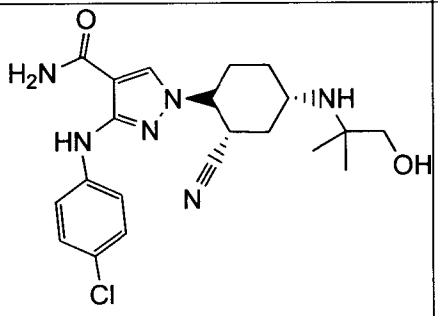
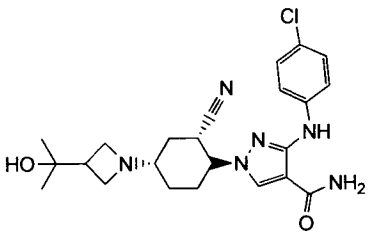
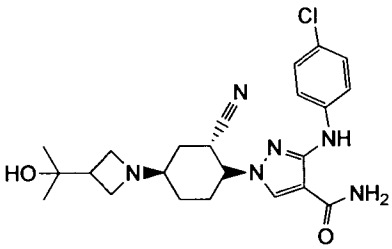
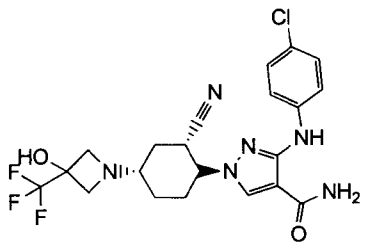
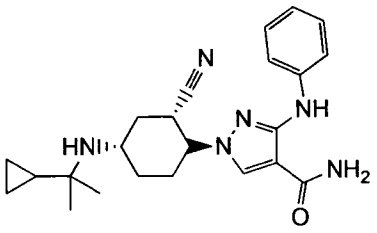
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
			nyl}amino)-1*H*-pyrazole-4-carboxamide	
28-185	**40**		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-{[(1S)-1-cyclopropylethyl]amino}cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 525, found 525
28-186	**40**		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3-methylazetidin-1-yl)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 511, found 511
28-187	**40**		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(3-methylazetidin-1-yl)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 511, found 511
28-188	**40**		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(dimethylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 421, found 421
28-189	**40**		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(dimethylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 421, found 421

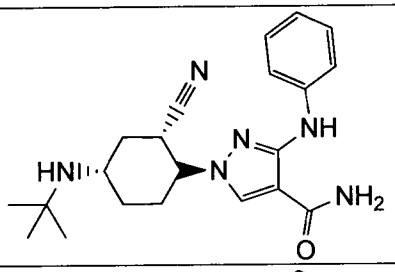
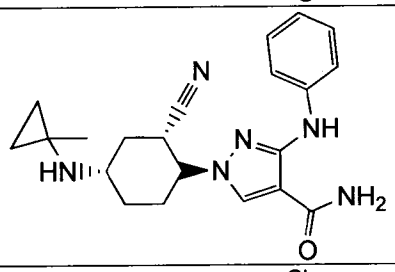
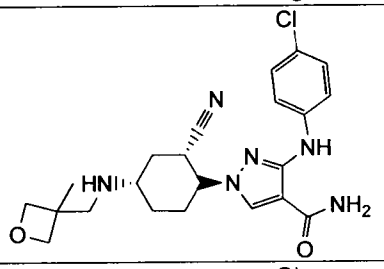
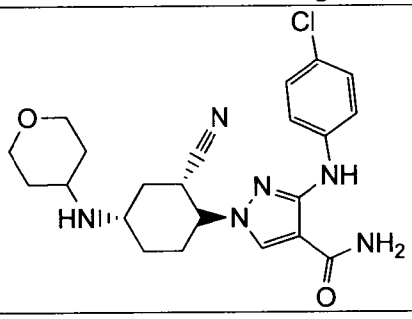
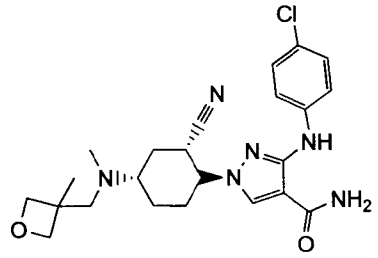
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-190	40		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-{[(1S)-1-cyclopropylethyl]amino}cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 461, found 461
28-191	40		1-[(1S,2S or 1R,2R)-2-cyano-4-{[(1S)-1-cyclopropylethyl]amino}cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 461, found 461
28-192	41		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]amino}cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 515, found 515
28-193	41		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-{[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]amino}cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 515, found 515
28-194	41		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]amino}cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 515, found 515

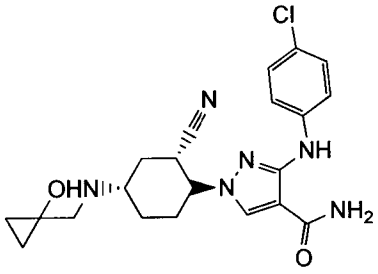
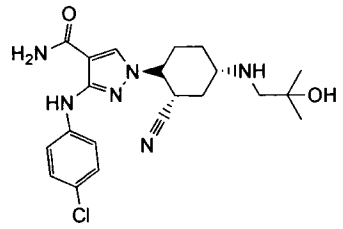
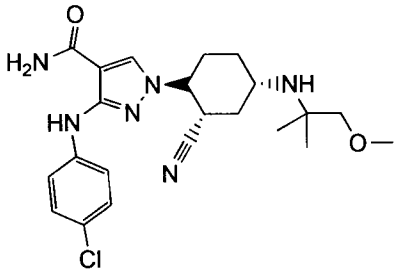
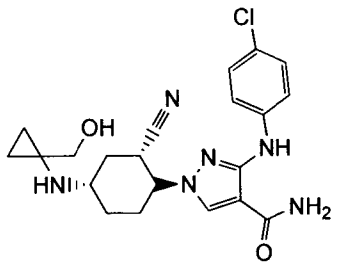
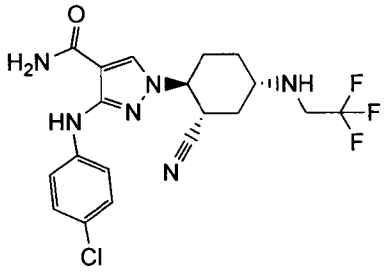
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-195	41		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-{[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]amino}cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 515, found 515
28-196	40		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(2,2-dimethylazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 461, found 461
28-197	40		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(2,2-dimethylazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 461, found 461
28-198	40		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3-hydroxy-3-methylazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 463, found 463
28-199	40		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(3-hydroxy-3-methylazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 463, found 463

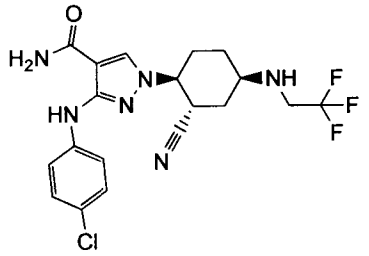
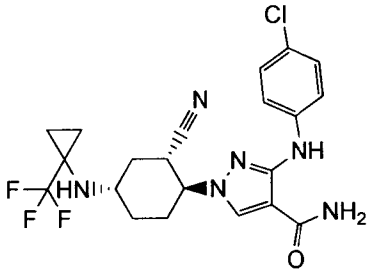
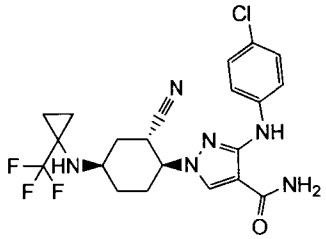
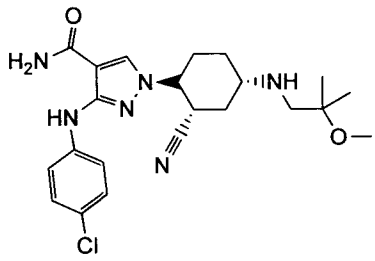
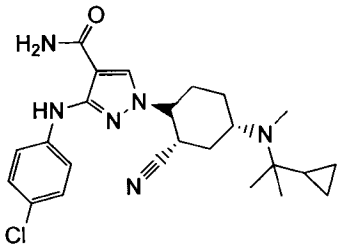
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-200	40		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[3-hydroxy-3-(trifluoromethyl)azetidin-1-yl]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 517, found 517
28-201	40		1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[3-hydroxy-3-(trifluoromethyl)azetidin-1-yl]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 517, found 517
28-202	40		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 461, found 461
28-203	40		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 461, found 461
28-204	43		1-[(1S,2S,4S or 1R,2R,4R)-4-(tert-butylamino)-2-cyanocyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 449, found 449

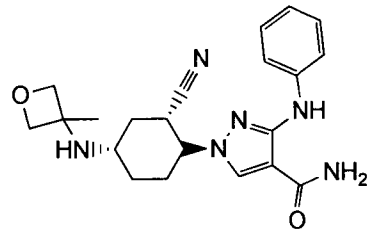
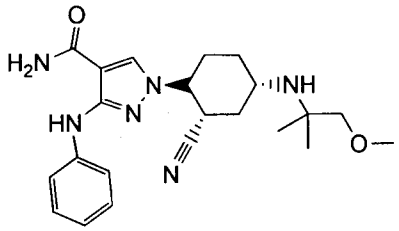
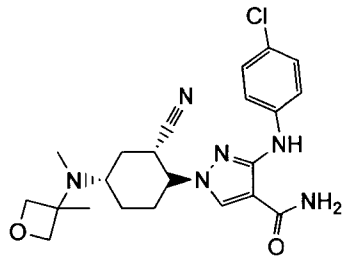
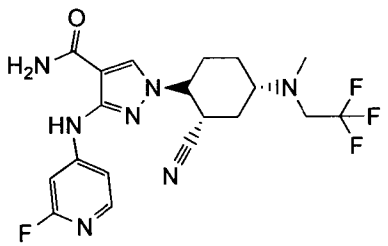
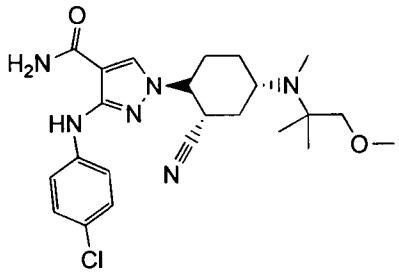
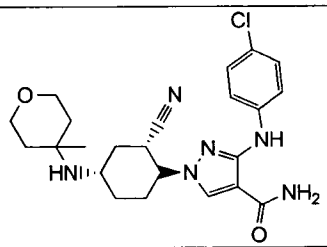
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-205	43		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R,)-2-cyano-4-[(1-methylcyclopropyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 413, found 413
28-206	43		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[(1-methylcyclopropyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 413, found 413
28-207	43		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(3-methyloxetan-3-yl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 429, found 429
28-208	43		3-[(4-chlorophenyl)amino]-1-{(1S,2S or 1R,2R)-2-cyano-4-[(1-cyclopropyl-1-methylethyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 441, found 441
28-209	43		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[(1-cyclopropyl-1-methylethyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 441, found 441

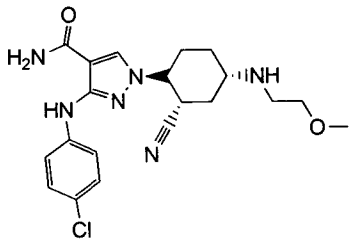
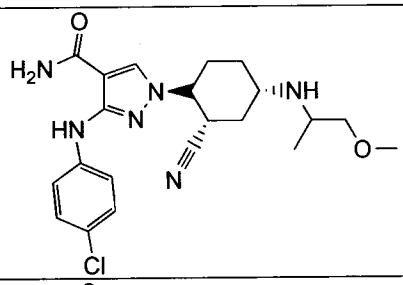
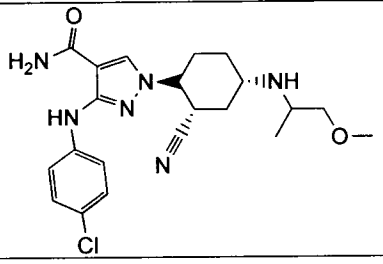
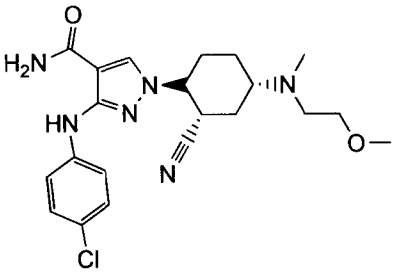
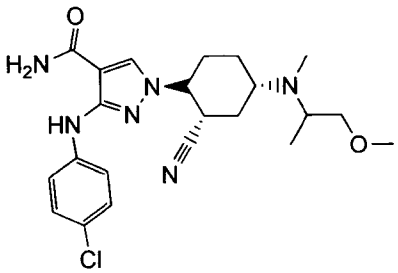
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-210	43		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2-hydroxy-1,1-dimethylethyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 431, found 431
28-211	43		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[3-(1-hydroxy-1-methylethyl)azetidin-1-yl]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 457, found 457
28-212	43		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[3-(1-hydroxy-1-methylethyl)azetidin-1-yl]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 457, found 457
28-213	43		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[3-hydroxy-3-(trifluoromethyl)azetidin-1-yl]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 483, found 483
28-214	43		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(1-cyclopropyl-1-methylethyl)amino]cyclohexyl}-3-(phenylamino)-1H-pyrazole-4-carboxamide	Calc'd 407, found 407

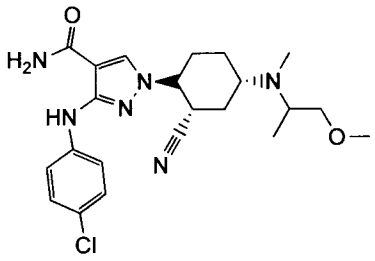
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-215	43		1-[(1S,2S,4S or 1R,2R,4R)-4-(tert-butylamino)-2-cyanocyclohexyl]-3-(phenylamino)-1H-pyrazole-4-carboxamide	Calc'd 381, found 381
28-216	43		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(1-methylcyclopropyl)amino]cyclohexyl}-3-(phenylamino)-1H-pyrazole-4-carboxamide	Calc'd 379, found 379
28-217	43		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(3-methyloxetan-3-yl)methyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide	Calc'd 443, found 443
28-218	43		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]-1H-pyrazole-4-carboxamide	Calc'd 443, found 443
28-219	43		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{methyl[(3-methyloxetan-3-yl)methyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide	Calc'd 457, found 457

Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-220	43		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(1-hydroxycyclopropyl)methyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide	Calc'd 429, found 429
28-221	43		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2-hydroxy-2-methylpropyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 431, found 431
28-222	43		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2-methoxy-1,1-dimethylethyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 445, found 445
28-223	43		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[1-(hydroxymethyl)cyclopropyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide	Calc'd 429, found 429
28-224	41		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2,2,2-trifluoroethyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 441, found 441

Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-225	41		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[(2,2,2-trifluoroethyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 441, found 441
28-226	41		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[1-(trifluoromethyl)cyclopropyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide	Calc'd 467, found 467
28-227	41		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-{[1-(trifluoromethyl)cyclopropyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide	Calc'd 467, found 467
28-228	43		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2-methoxy-2-methylpropyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 445, found 445
28-229	44		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(1-cyclopropyl-1-methylethyl)(methyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 455, found 455

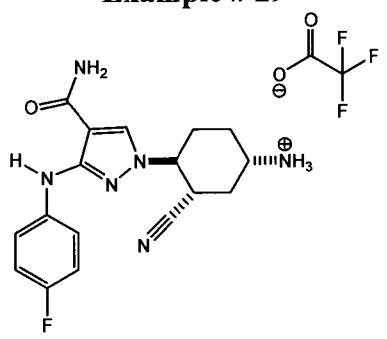
Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-230	43		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(3-methyloxetan-3-yl)amino]cyclohexyl}-3-(phenylamino)-1H-pyrazole-4-carboxamide	Calc'd 395, found 395
28-231	43		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2-methoxy-1,1-dimethylethyl)amino]cyclohexyl}-3-(phenylamino)-1H-pyrazole-4-carboxamide	Calc'd 411, found 411
28-232	44		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[methyl(3-methyloxetan-3-yl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 443, found 443
28-233	44		1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[methyl(2,2,2-trifluoroethyl)amino]cyclohexyl}-3-[(2-fluoropyridin-4-yl)amino]-1H-pyrazole-4-carboxamide	Calc'd 440, found 440
28-234	44		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2-methoxy-1,1-dimethylethyl)(methyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 459, found 459
28-235	43		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(4-methyltetrahydro-2H-pyran-4-yl)amino]cyclohexyl}-1H-	Calc'd 457, found 457

Example	Method	Structure	Compound Name	Exact Mass [M+H]+
			pyrazole-4-carboxamide	
28-236	43		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2-methoxyethyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 417, found 417
28-237	43		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(1S)-2-methoxy-1-methylethyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide	Calc'd 431, found 431
28-238	43		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(1S)-2-methoxy-1-methylethyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide	Calc'd 431, found 431
28-239	44		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2-methoxyethyl)(methyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide	Calc'd 431, found 431
28-240	44		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(1S or 1R)-2-methoxy-1-methylethyl](methyl)amino}cyclohexyl]-1H-pyrazole-4-carboxamide	Calc'd 445, found 445

Example	Method	Structure	Compound Name	Exact Mass [M+H]+
28-241	44		3-[(4-chlorophenyl)amino]-1-[(1R,2S,4S1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(1S or 1R)-2-methoxy-1-methylethyl](methyl)amino}cyclohexyl]-1H-pyrazole-4-carboxamide	Calc'd 445, found 445

Scheme #56

Example # 29



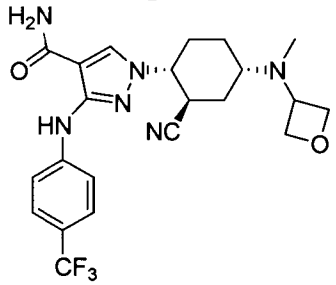
Step A-C: **(1S,3S,4S and 1R,3R,4R)-4-{4-Carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexanaminium trifluoroacetate**

1-[(1S,2S,4R and 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-[(fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide (**Example #5**, 50 mg, 0.15 mmol) was dissolved in DCM (1.5 mL) and cooled to 0 °C. TEA (0.041 mL, 0.29 mmol) and methanesulfonyl chloride (0.014 mL, 0.18 mmol) were added sequentially and the reaction mixture was maintained at 0 °C for 10 minutes. The reaction mixture was then partitioned between saturated aqueous $NaHCO_3$ and EtOAc, the layers were separated, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue, which was carried on without further purification, was dissolved in DMF (0.72 mL) followed by the addition of sodium azide (94 mg, 1.5 mmol). The reaction mixture was heated to 90 °C for 16 hours. After cooling to ambient temperature the reaction mixture was partitioned between water and EtOAc. The layers were separated, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue, which was carried on without further purification, was dissolved in THF (1.9 mL). Triphenylphosphine (145 mg, 0.554 mmol) and water (0.033 mL, 1.9 mmol) were added and the

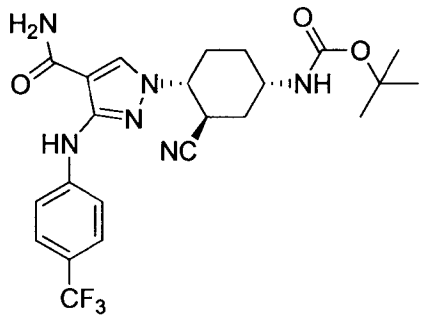
reaction mixture was heated to 55 °C for 20 hours. The reaction mixture was then allowed to cool to ambient temperature, filtered, and purified by reverse phase preparative HPLC (using a gradient elution of 20-60% MeCN/water, with 0.1% v/v TFA modifier). Desired fractions were identified, combined, and lyophilized to afford the title compound. ^{1}H NMR (DMSO-d_6): δ 9.13 (s, 1H), 8.21 (s, 1H), 8.04 (br s, 3H), 7.70 (br s, 1H), 7.53 (m, 2H), 7.17 (br s, 1H), 7.05 (m, 2H), 4.49 (ddd, J = 11.5, 11.5, 4 Hz, 1H), 3.58 (ddd, J = 13, 13, 4 Hz, 1H), 3.28 (br s, 1H), 2.37 (d, J = 11.5 Hz, 1H), 2.01 (m, 3H), 1.84 (ddd, J = 12.5, 12.5, 12.5 Hz, 1H), 1.55 (m, 1H). LRMS (ESI) calc'd for $C_{17}H_{19}FN_6O$ $[M+H]^+$: 343, Found: 343.

Scheme #50

Example #30-1



1-{(1R,2R,4S or 1S,2S,4R)-2-Cyano-4-[methyl(oxetan-3-yl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide

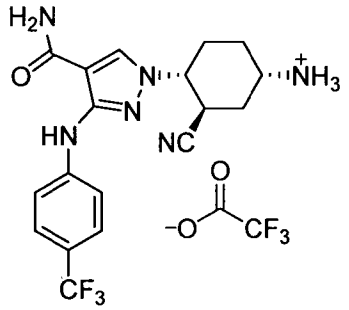


Step A: ***tert*-Butyl ((1S,3R,4R or 1R,2S,4S)-4-(4-carbamoyl-3-((4-(trifluoromethyl)phenyl)amino)-1*H*-pyrazol-1-yl)-3-cyanocyclohexyl)carbamate**

To a solution of tert-butyl [(1R,3S,4S and 1S,3R,4R)-4-(3-amino-4-carbamoyl-1*H*-pyrazol-1-yl)-3-cyanocyclohexyl]carbamate (4.74 g, 13.6 mmol) in 2-propanol (68 mL), were added 1-bromo-4-(trifluoromethyl)benzene (3.67 g, 16.3 mmol), potassium acetate (2.67 g, 27.2 mmol), tetramethyl *t*-butyl X-Phos (1.96 g, 4.08 mmol), and Pd_2dba_3 (1.87 g, 2.04 mmol). The reaction was degassed by bubbling argon gas for 10 minutes, sealed, and heated to 90 °C for 14 hours. The reaction mixture was cooled to ambient temperature and partitioned between EtOAc and brine. The organic layer was collected, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (Using a gradient elution

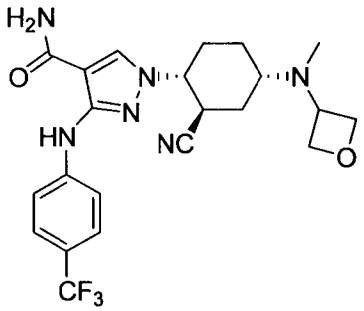
of 0-100% EtOAc/hexanes) to afford *tert*-butyl [(1R,3S,4S and 1S,3R,4R)-4-(4-carbamoyl-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazol-1-yl)-3-cyanocyclohexyl]carbamate as a racemic mixture. The racemate was resolved via chiral SFC chromatography (Chiral Technology IC 2.1X 25 cm column, mobile phase:15%/85% Methanol/CO_2) to afford the separated enantiomers.

Intermediate A of Example #30-1: The 2nd enantiomer to elute; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.45 (s, 1H), 8.27 (s, 1H), 7.69 (d, J = 9 Hz, 2H), 7.53 (d, J = 9 Hz, 2H), 7.20 (s, 2H), 4.45-4.40 (td, J = 10.8, 3.6 Hz, 1H), 3.70 (m, 1H), 3.64-3.60 (td, J = 11.4, 3.6 Hz, 1H), 2.09-1.94 (m, 3H), 1.83-1.80 (m, 2H), 1.68-1.63 (m, 1H), 1.38 (s, 9H). LRMS (ESI) calc'd for $C_{23}H_{28}F_3N_6O_3$ $[M+H]^+$: 493, Found: 493.



Step B: **(1R,3S,4S or 1S, 3R, 4R)-4-(4-carbamoyl-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazol-1-yl)-3-cyanocyclohexanaminium trifluoroacetate**

tert-Butyl ((1S,3R,4R or 1R,2S,4S)-4-(4-carbamoyl-3-((4-(trifluoromethyl)phenyl)amino)-1*H*-pyrazol-1-yl)-3-cyanocyclohexyl)carbamate (**Intermediate B of Example #30-1**, 640 mg, 1.30 mmol) was dissolved in DCM (3 mL) at 0 °C and TFA (3 mL) was added. The solution was stirred for 1 hour then concentrated *in vacuo* to afford the title compound. LRMS (ESI) calc'd for $C_{18}H_{20}F_3N_6O$ $[M+H]^+$: 393, Found: 393.



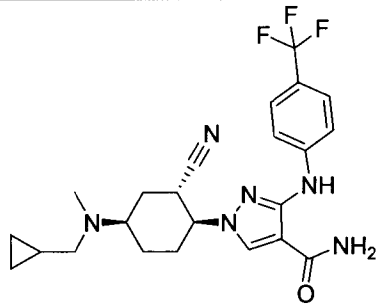
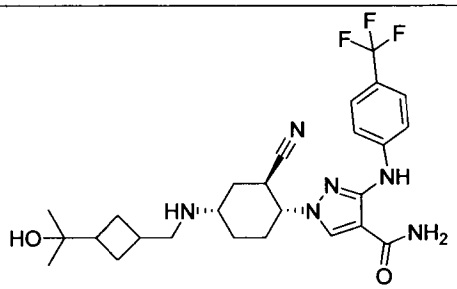
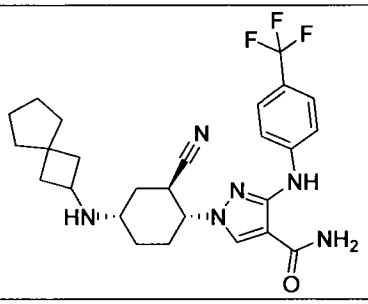
Step C: **1-{(1R,2R,4S or 1S,2S,4R)-2-Cyano-4-[methyl(oxetan-3-yl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide**

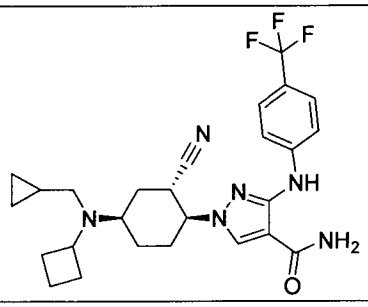
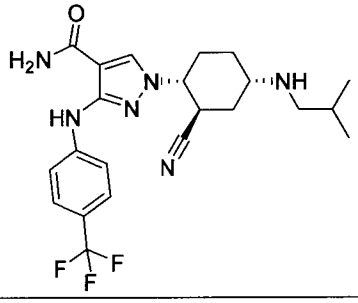
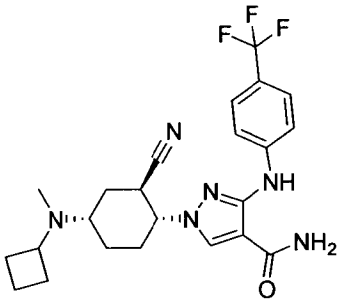
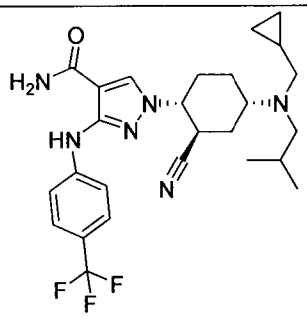
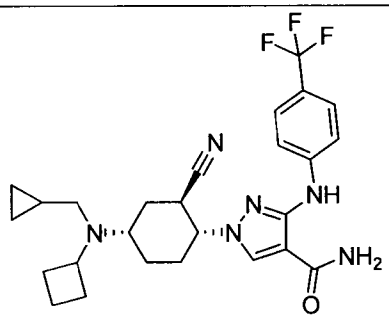
To a solution of (1R,3S,4S or 1S,3R,4R)-4-(4-carbamoyl-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazol-1-yl)-3-cyanocyclohexanaminium trifluoroacetate (30 mg, 0.059 mmol) in DMF (0.5 mL) and MeOH (0.5 mL) were added oxetan-3-one (21 mg, 0.30 mmol) and stirred for 15 minutes followed by sodium cyanoborohydride (9 mg, 0.3 mmol).

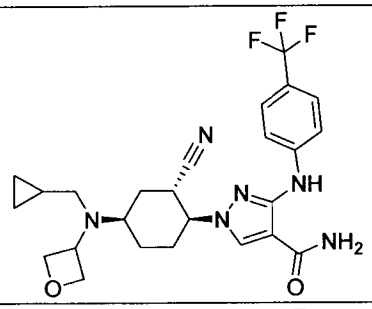
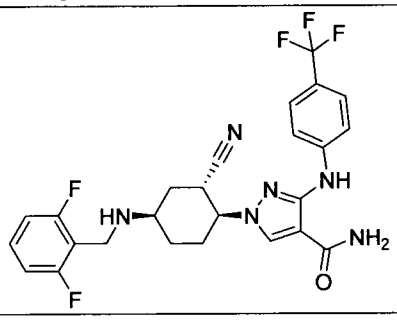
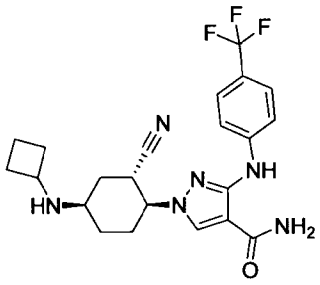
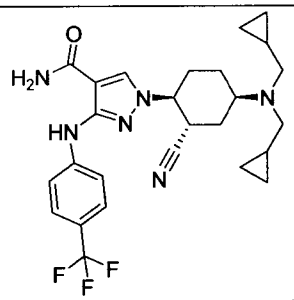
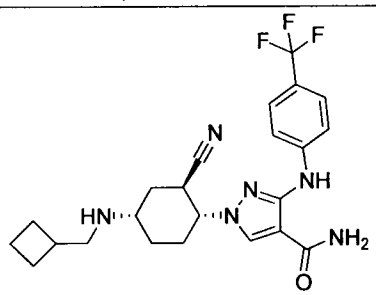
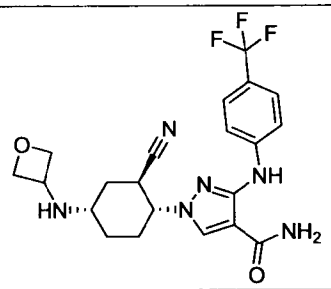
Additional oxetan-3-one (13 mg, 0.18 mmol) was added and the reaction mixture was stirred for 15 minutes then additional sodium cyanoborohydride (9 mg, 0.3 mmol) was added. After 30 minutes formaldehyde (48 mg, 0.59 mmol) was added and the mixture was stirred for 15 minutes before additional sodium cyanoborohydride (9 mg, 0.3 mmol) was added. The reaction was stirred for 1 hour then filtered and purified directly by reverse phase HPLC to afford the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 8.22 (s, 1H), 7.68 (d, J = 9 Hz, 2H) 7.53 (d, 8.5 Hz, 2H), 4.74-4.64 (m, 4H), 4.47 (m, 1H), 4.04-4.02 (m, 1H), 3.86 (m, 1H), 2.65 (m, 1H), 2.40 (m, 1H), 2.24 (s, 3H), 2.16 (m, 1H), 2.06 (m, 1H), 1.97-1.88 (m 2H), 1.70 (m, 1H). LRMS (ESI) calc'd for $C_{22}H_{26}F_3N_6O_2$ $[M+H]^+$: 463, Found: 463.

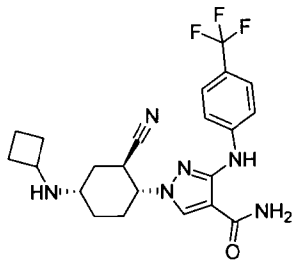
The following compounds shown in **TABLE 24** were prepared according to **Scheme #50** following similar procedures described for **Example #30-1** which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 24:

Example	Structure	Compound Name	Exact Mass [M+H]+
30-2		1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[(cyclopropylmethyl)(methyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 461, found 461
30-4		1-[(1R,2R,4S or 1S,2S,4R)-2-cyano-4-({[3-(1-hydroxy-1-methylethyl)cyclobutyl]methyl}amino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 519, found 519
30-5		1-[(1R,2R,4S or 1S,2S,4R)-2-cyano-4-(spiro[3.4]oct-2-ylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 501, found 501

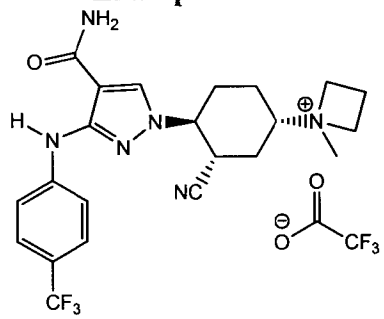
30-6		1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[cyclobutyl(cyclopropylmethyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 501, found 501
30-7		1-{(1R,2R,4S or 1S,2S,4R)-2-cyano-4-[(2-methylpropyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 449, found 449
30-8		1-{(1R,2R,4Sor 1S,2S,4R)-2-cyano-4-[cyclobutyl(methyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 461, found 461
30-9		1-{(1R,2R,4Sor 1S,2S,4R)-2-cyano-4-[(cyclopropylmethyl)(2-methylpropyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 503, found 503
30-10		1-{(1R,2R,4S or 1S,2R,4R)-2-cyano-4-[cyclobutyl(cyclopropylmethyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 501, found 501

30-12		1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[(cyclopropylmethyl)(oxetan-3-yl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 503, found 503
30-13		1-{(1S,2S,4R or 1R,2R,4S)-2-cyano-4-[(2,6-difluorobenzyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 519, found 519
30-14		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-(cyclobutylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 447, found 447
30-15		1-{(1S,2S,4R or 1R,2R,4S)-4-[bis(cyclopropylmethyl)amino]-2-cyanocyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 501, found 501
30-16		1-{(1R,2R,4S or 1S,2S,4R)-2-cyano-4-[(cyclobutylmethyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 461, found 461
30-17		1-[(1R,2R,4S or 1S,2S,4R)-2-cyano-4-(oxetan-3-ylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 449, found 449

30-18		1-[(1R,2R,4S or 1S,2S,4R)-2-cyano-4-(cyclobutylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 447, found 447

Scheme #45

Example #31-1

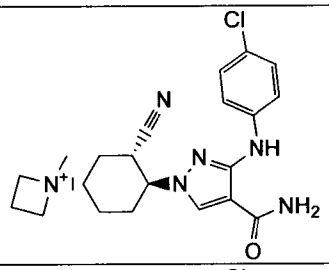
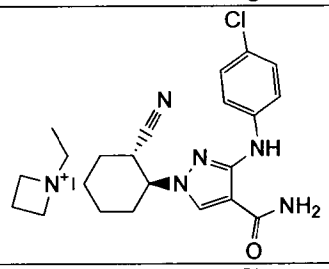
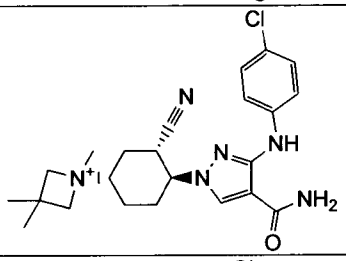
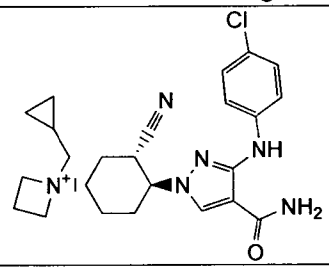


1-((1S,3S,4S or 1R,3R,4R)-4-(4-carbamoyl-3-((4-(trifluoromethyl)phenyl)amino)-1*H*-pyrazol-1-yl)-3-cyanocyclohexyl)-1-methylazetidin-1-ium 2,2,2-trifluoroacetate

Iodomethane (0.011 mL, 0.17 mmol) was added to a mixture of 1-((1S,2S,4S or 1R,2R,4R)-4-(Azetidin-1-yl)-2-cyanocyclohexyl)-3-((4-(trifluoromethyl)phenyl)amino)-1*H*-pyrazole-4-carboxamide (**Example #28-1,** 15 mg, 0.034 mmol) and DIPEA (0.006 mL, 0.03 mmol) in MeCN (0.70 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 2 hours, and was then purified directly by reverse-phase preparative HPLC (using a gradient elution of MeCN/water, with 0.1% v/v TFA modifier). Desired fractions were identified, combined, and lyophilized to afford the title compound. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.59 (s, 1H), 8.30 (s, 1H), 7.82 (s, 1H), 7.10 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H), 7.31 (s, 1H), 4.60-4.49 (m, 3H), 4.11-3.90 (m, 2H), 3.80-3.48 (m, 4H), 2.78-2.70 (m, 1H), 2.40-2.37 (m, 1H), 2.29-2.23 (m, 1H), 2.19-2.16 (m, 1H), 2.10-1.96 (m, 3H), 1.68-1.62 (m, 1H). LRMS (ESI) calc'd for $C_{22}H_{26}F3N_6O^+$ $[M]^+$: 447, Found: 447.

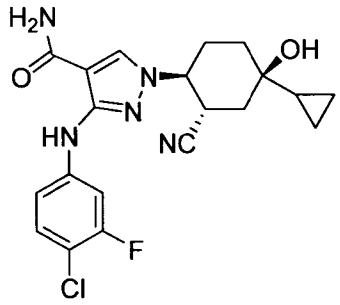
The following compounds shown in **TABLE 25** were prepared according to **Scheme #45** following similar procedures described for **Example #31-1** which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 25:

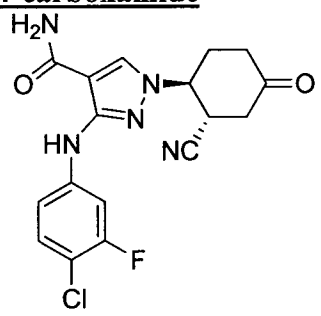
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
31-2		1-[(1S,3S,4S)-4-{4-carbamoyl-3-[(4-chlorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl]-1-methylazetidinium	Calc'd 413, found 413
31-3		1-[(1S,3S,4S)-4-{4-carbamoyl-3-[(4-chlorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl]-1-ethylazetidinium	Calc'd 427, found 427
31-4		1-[(1S,3S,4S)-4-{4-carbamoyl-3-[(4-chlorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl]-1,3,3-trimethylazetidinium	Calc'd 441, found 441
31-5		1-[(1S,3S,4S)-4-{4-carbamoyl-3-[(4-chlorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl]-1-(cyclopropylmethyl)azetidinium	Calc'd 453, found 453

Scheme #38

Example #32-1



3-[(4-Chloro-3-fluorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-cyclopropyl-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide



Step A: 3-((4-Chloro-3-fluorophenyl)amino)-1-((1S,2S or 1R,2R)-2-cyano-4-oxocyclohexyl)-1*H*-pyrazole-4-carboxamide

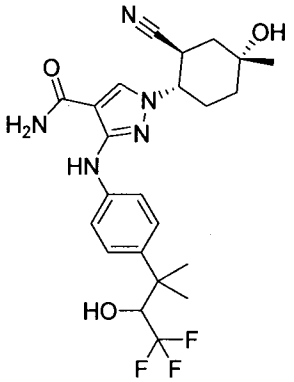
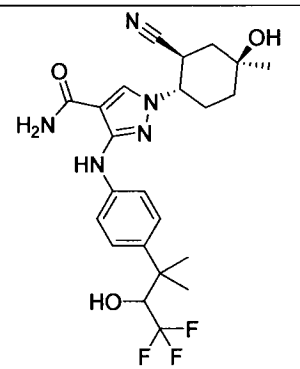
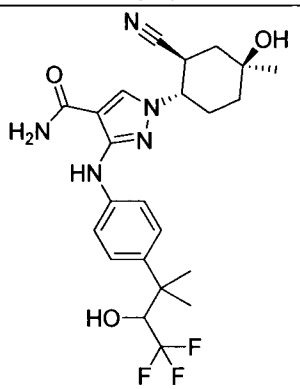
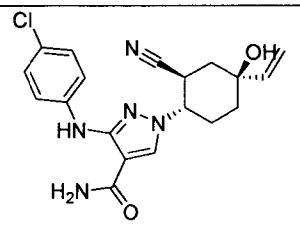
According to the oxidation protocol described for **Example #27-1** and **#27-2**, 3-[(4-chloro-3-fluorophenyl)amino]-1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide (**Example #25-3**) was converted to 3-[(4-chloro-3-fluorophenyl)amino]-1-[(1*S*,2*S* or 1*R*,2*R*)-2-cyano-4-oxocyclohexyl]-1*H*-pyrazole-4-carboxamide under the action of TPAP and NMO. LRMS (ESI) calc'd for $C_{17}H_{15}ClFN_5O_2$ $[M+H]^+$: 376, Found: 376.

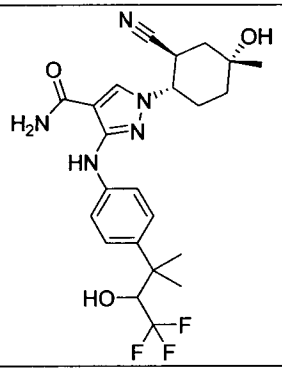
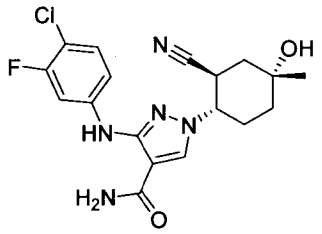
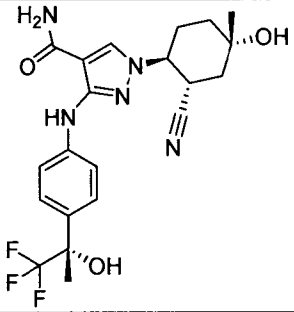
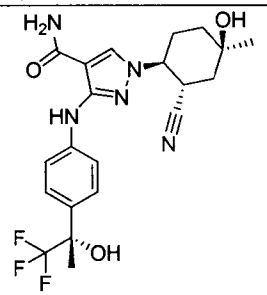
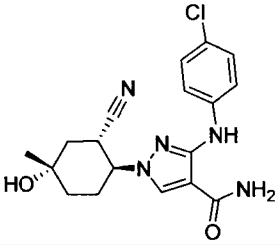
Step B: 3-[(4-Chloro-3-fluorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-cyclopropyl-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide

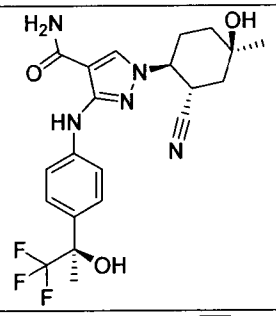
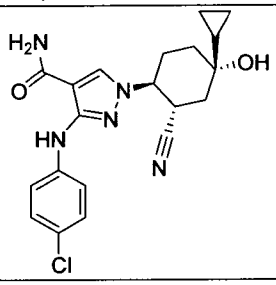
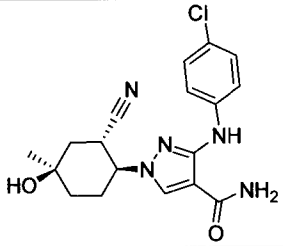
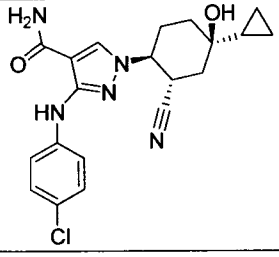
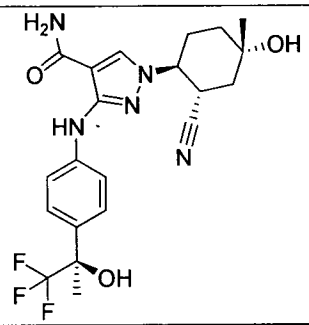
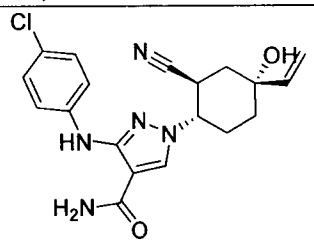
To a solution of 3-[(4-chloro-3-fluorophenyl)amino]-1-[(1*S*,2*S* or 1*R*,2*R*)-2-cyano-4-oxocyclohexyl]-1*H*-pyrazole-4-carboxamide (209 mg, 0.556 mmol) in THF (5.6 mL) at -78 °C under argon was added cyclopropyl magnesium bromide solution (6.67 mL, 3.34 mmol, 0.5 M in THF) dropwise. The solution was maintained at -78 °C for 45 minutes then another 3 eq. cyclopropyl magnesium bromide (3.33 mL, 1.67 mmol, 0.5 M in THF) was added dropwise. The solution was stirred at -78 °C for 1 hour then warmed to -30 °C and quenched with saturated aqueous ammonium chloride followed by warming to ambient temperature. The solution was taken up in EtOAc. The organic layer was washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The reaction mixture was purified by MPLC on silica gel (using a gradient elution of 0-8% MeOH/DCM) to afford a mixture of diastereomers. The diastereomers were separated by reverse phase preparative HPLC to afford the title compound. ^1H NMR (500 MHz, CD_3OD): δ 8.15 (s, 1H), 7.78-7.75 (dd, J = 13, 3 Hz, 1H), 7.27-7.23 (t, J = 9 Hz, 1H), 7.12-7.09 (m 1H), 4.35-4.30 (td, J = 12, 4 Hz, 1H), 3.68-3.62 (m, 1H), 2.47-2.42 (qd, J = 13, 4 Hz, 1H), 2.15-2.10 (dt, J = 14, 4 Hz, 1 H), 1.98-190 (m, 2H), 1.82-1.78 (m, 1H), 1.72-1.65 (td, J = 14, 5 Hz, 1H), 0.92-0.87 (m, 1 H), 0.437-0.360 (m, 3H). LRMS (ESI) calc'd for $C_{20}H_{22}ClFN_5O_2$ $[M+H]^+$: 418, Found: 418.

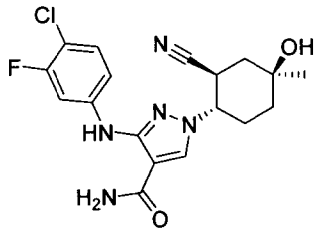
The following compounds shown in **TABLE 26** were prepared according to **Scheme #38** following similar procedures described for **Example #32-1** which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 26:

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
32-2		**1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxy-4-methylcyclohexyl]-3-{[4-(3,3,3-trifluoro-(2R or 2S)-hydroxy-1,1-dimethylpropyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide**	**Calc'd 480, found 480**
32-3		**1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxy-4-methylcyclohexyl]-3-{[4-(3,3,3-trifluoro-(2R or 2S)-hydroxy-1,1-dimethylpropyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide**	**Calc'd 480, found 480**
32-4		**1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxy-4-methylcyclohexyl]-3-{[4-(3,3,3-trifluoro-(2R or 2S)-hydroxy-1,1-dimethylpropyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide**	**Calc'd 480, found 480**
32-5		**3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-ethenyl-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide**	**Calc'd 386, found 386**

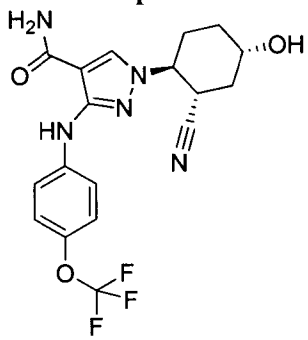
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
32-6		1-[(1S,2S,4R or 1R,2R,4R)-2-cyano-4-hydroxy-4-methylcyclohexyl]-3-{[4-(3,3,3-trifluoro-(2R or 2S)-hydroxy-1,1-dimethylpropyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 480, found 480
32-7		3-[(4-chloro-3-fluorophenyl)amino]-1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxy-4-methylcyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 392, found 392
32-8		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxy-4-methylcyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 452, found 452
32-9		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxy-4-methylcyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 452, found 452
32-10		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxy-4-methylcyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 374, found 374

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
32-11		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxy-4-methylcyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 452, found 452
32-12		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-cyclopropyl-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 400, found 400
32-13		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxy-4-methylcyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 374, found 374
32-14		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-cyclopropyl-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 400, found 400
32-15		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxy-4-methylcyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 452, found 452
32-16		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-ethenyl-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 386, found 386

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
32-17		3-[(4-chloro-3-fluorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxy-4-methylcyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 392, found 392

Scheme #39

Example #33-1



1-((1S,2S,4S or 1R,2R,4R)-2-Cyano-4-hydroxycyclohexyl)-3-((4-(trifluoromethoxy)phenyl)amino)-1*H*-pyrazole-4-carboxamide

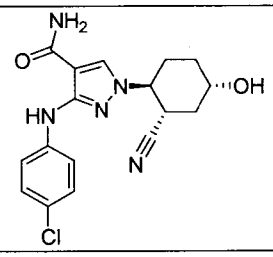
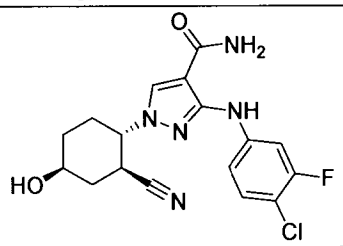
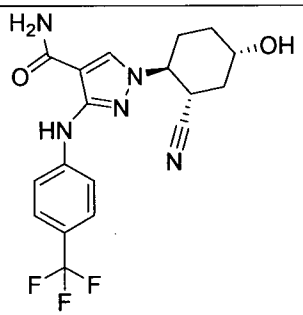
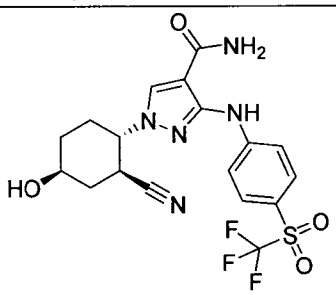
According to oxidation protocol described for **Example #27-1** and **27-#2**, 1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-{[4-(trifluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide (**Example #25-5**) was converted to 1-((1S,2S or 1R,2R)-2-cyano-4-oxocyclohexyl)-3-((4-(trifluoromethoxy)phenyl)amino)-1*H*-pyrazole-4-carboxamide under the action of TPAP and NMO.

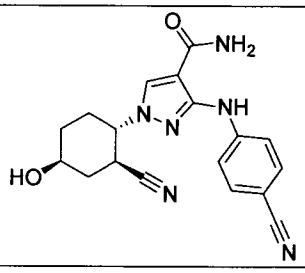
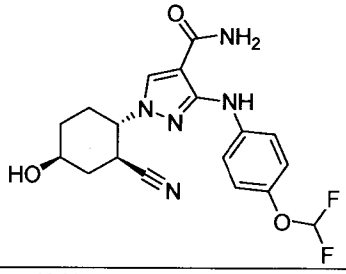
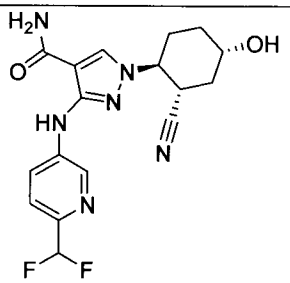
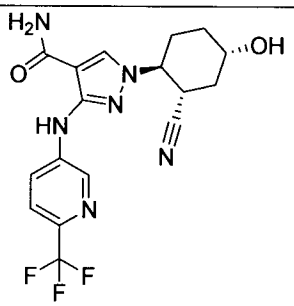
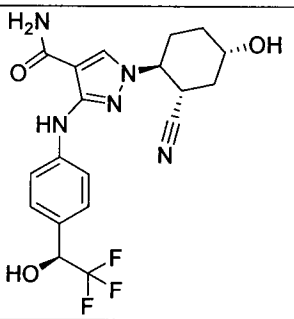
1-((1S,2S or 1R,2R)-2-cyano-4-oxocyclohexyl)-3-((4-(trifluoromethoxy)phenyl)amino)-1*H*-pyrazole-4-carboxamide (1.35 g, 3.31 mmol) was dissolved in methanol (16 mL) and sodium borohydride (0.125 g, 3.31 mmol) was added. The resulting mixture was stirred for 1 hour. The reaction mixture was diluted with EtOAc and the organic layer was collected, washed with water, brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 0-10% MeOH/DCM) to afford mixture of diastereomers. The diastereomers were separated by chiral SFC purification (Chiral Technology IB 2.1 X 25cm, 5uM column, mobile phase: 20% methanol/CO_2) to afford the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.26 (s, 1H), 8.22 (s, 1 H), 7.69 (br, 1H), 7.62 – 7.60 (d, 2H), 7.22 – 7.21 (d, 2H), 7.18 (br, 1H), 5.00 – 4.99 (d, 1H), 4.45 – 4.39 (m, 1H), 3.60 – 3.55 (m, 1H), 3.44 – 3.39 (m, 1H), 2.24 – 2.22 (m, 1H), 1.93 –

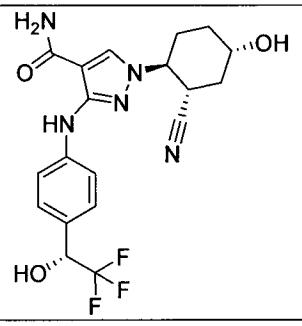
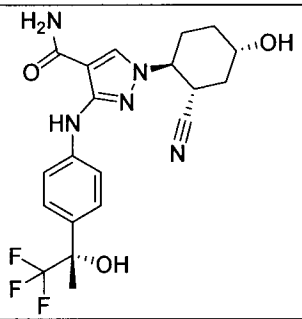
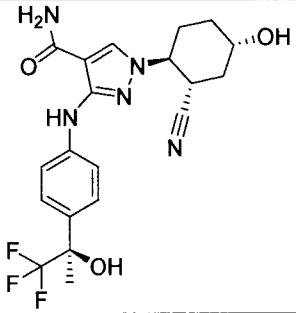
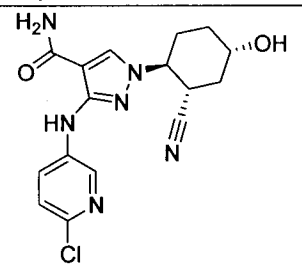
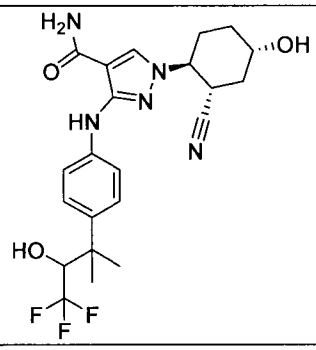
1.88 (m, 3H), 1.69 – 1.61 (m, 1H), 1.45 – 1.37 (m, 1H). LRMS (ESI) calc'd [M+H]+: 410, Found: 410.

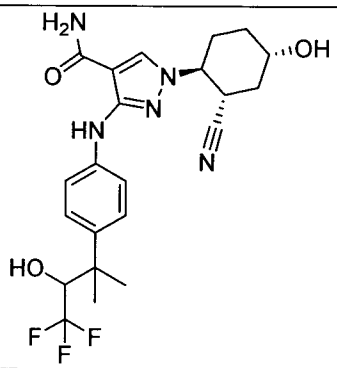
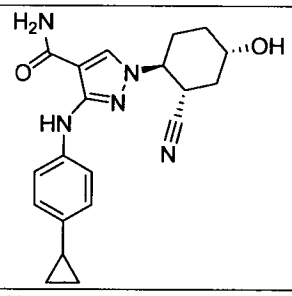
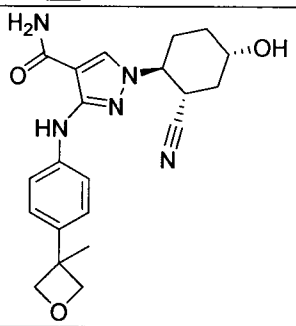
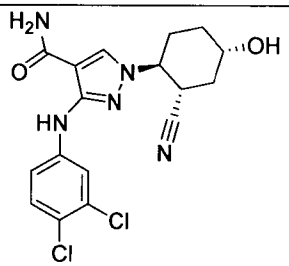
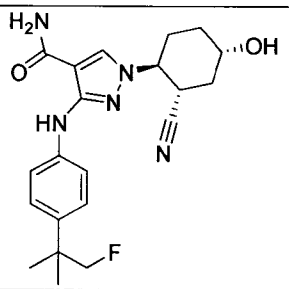
The following compounds shown in **TABLE 27** were prepared according to **Scheme #39** following similar procedures described for **Example #33-1**, which can be achieved by those of ordinary skill in the art of organic synthesis.

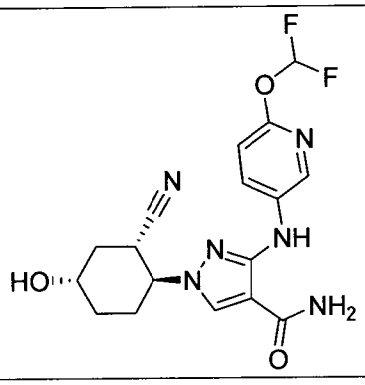
TABLE 27:

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
33-2		**3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide**	**Calc'd 360, found 360**
33-3		**3-[(4-chloro-3-fluorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide**	**Calc'd 378, found 378**
33-4		**1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide**	**Calc'd 394, found 394**
33-5		**1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide**	**Calc'd 458, found 458**

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
33-6		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-[(4-cyanophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 351, found 351
33-7		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-{[4-(difluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 392, found 392
33-8		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-{[6-(difluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 377, found 377
33-9		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 395, found 395
33-10		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-({4-[(1S)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 424, found 424

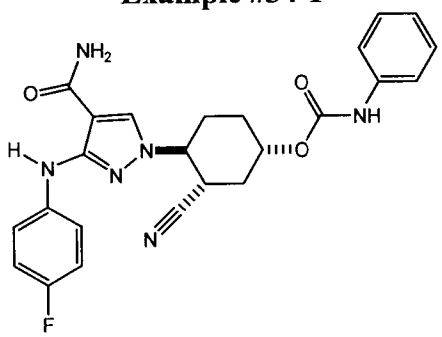
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
33-11		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 424, found 424
33-12		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 438, found 438
33-13		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 438, found 438
33-14		3-[(6-chloropyridin-3-yl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 361, found 361
33-15		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-{[4-(3,3,3-trifluoro-(2R or 2S)-hydroxy-1,1-dimethylpropyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 466, found 466

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
33-16		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-{[4-(3,3,3-trifluoro-(2R or 2S)-hydroxy-1,1-dimethylpropyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 466, found 466
33-18		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-[(4-cyclopropylphenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 366, found 366
33-19		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-{[4-(3-methyloxetan-3-yl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 396, found 396
33-20		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-[(3,4-dichlorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 394, found 394
33-21		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-{[4-(2-fluoro-1,1-dimethylethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 400, found 400

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
25-2		1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide	Calc'd 393, found 393

Scheme #52

Example #34-1

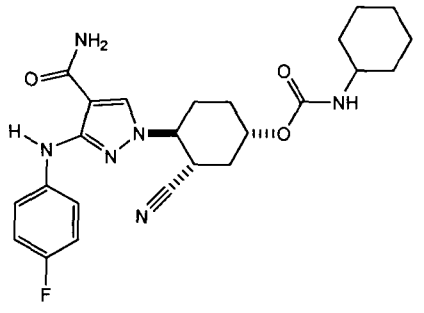
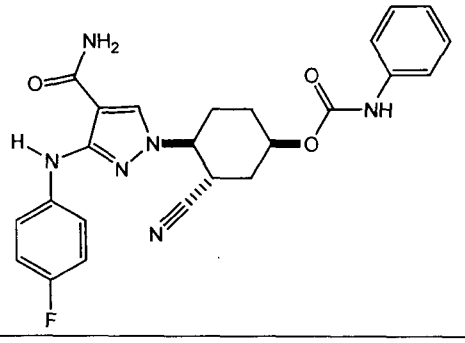
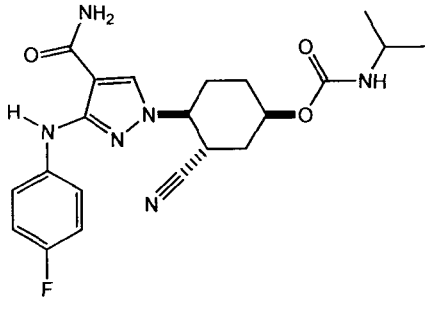
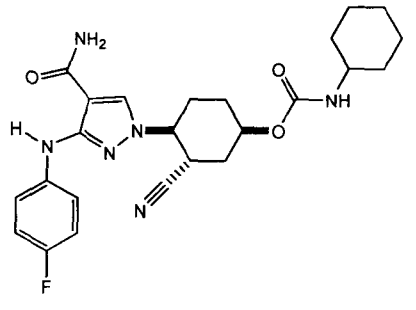


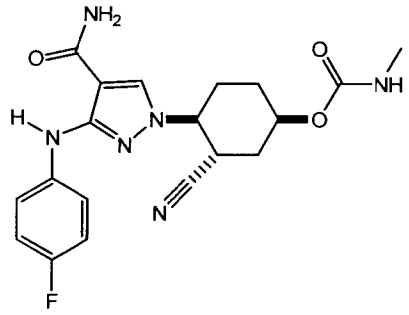
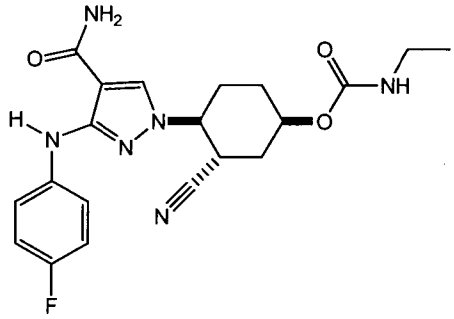
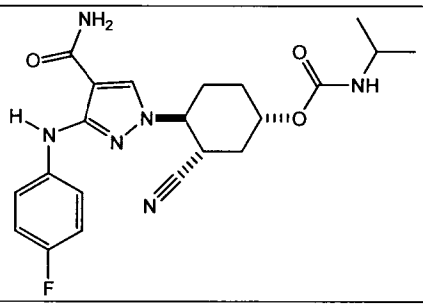
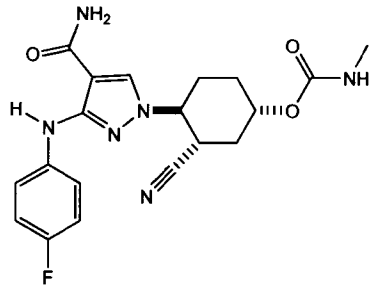
(1S,3S,4S and 1R,3R,4R)-4-{4-Carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl phenylcarbamate

To a solution of 1-[(1S,2S,4S and 1R,2R,4R)-2-cyano-4-hydroxycyclohexyl]- 3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide (25 mg, 0.073 mmol) in THF (0.73 mL) was added DMAP (9 mg, 0.07 mmol) and phenyl isocyanate (0.05 mL, 0.4 mmol). The resulting mixture was allowed to stir at ambient temperature for 24 hours. The reaction mixture was then partitioned between 0.5 N aqueous HCl and EtOAc. The organic layer was washed sequentially with water and brine. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by reverse phase preparative HPLC (using a gradient elution of 50-85% MeCN/water, with 0.1% v/v TFA modifier). Desired fractions were combined, partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The organic layer was collected, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title compound. ^{1}H NMR (DMSO-d_6): δ 9.71 (s, 1H), 9.12 (s, 1H), 8.21 (s, 1H), 7.70 (br s, 1H), 7.56 (m, 2H), 7.46 (d, J = 7.5 Hz, 2H), 7.27 (dd, J = 7.5, 7.5 Hz, 2H), 7.16 (br s, 1H), 7.07 (m, 2H), 6.98 (dd, J = 7.5, 7.5, Hz, 1H), 4.80 (m, 1H), 4.56 (m, 1H), 3.63 (m, 1H), 2.44 (m, 1H), 2.12-1.93 (m, 4H), 1.65 (m, 1H). LRMS (ESI) calc'd for $C_{24}H_{23}FN_6O_3$ $[M+H]^+$: 463, Found: 463.

The following compounds shown in **TABLE 28** were prepared according to **Scheme #52** following similar procedures described for **Example #34-1**, which can be achieved by those of ordinary skill in the art of organic synthesis.

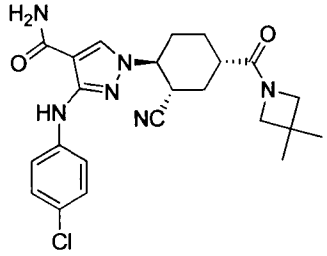
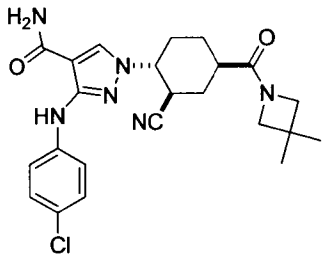
TABLE 28:

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
34-2		(1S,3S,4S and 1R,3R,4R)-4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl cyclohexylcarbamate	Calc'd 469, Found 469
34-3		(1R,3S,4S and 1S,3R,4R)-4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl phenylcarbamate	Calc'd 463, Found 463
34-4		(1R,3S,4S and 1S,3R,4R)-4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl propan-2-ylcarbamate	Calc'd 429, Found 429
34-5		(1R,3S,4S and 1S,3R,4R)-4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl cyclohexylcarbamate	Calc'd 469, Found 469

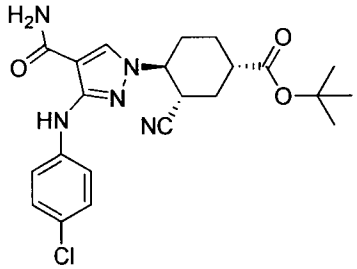
Example	Structure	Compound Name	Exact Mass $[M+H]^+$
34-6		(1R,3S,4S and 1S,3R,4R)-4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl methylcarbamate	Calc'd 401, Found 401
34-7		(1R,3S,4S and 1S,3R,4R)-4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl ethylcarbamate	Calc'd 415, Found 415
34-8		(1S,3S,4S and 1R,3R,4R)-4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl propan-2-ylcarbamate	Calc'd 429, Found 429
34-9		(1S,3S,4S and 1R,3R,4R)-4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl methylcarbamate	Calc'd 401, Found 401

Scheme #48

Example #35-1 and 35-2

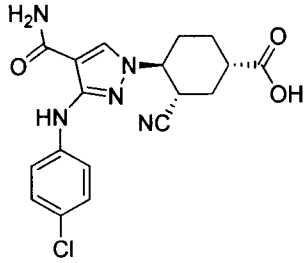



3-((4-chlorophenyl)amino)-1-((1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3,3-dimethylazetidine-1-carbonyl)cyclohexyl)-1*H*-pyrazole-4-carboxamide



Step A: **(1S,3S,4S and 1R,3R,4R)-*tert*-Butyl 4-(4-carbamoyl-3-((4-chlorophenyl)amino)-1*H*-pyrazol-1-yl)-3-cyanocyclohexanecarboxylate**

A solution of (1*S*,3*S*,4*S* and 1*R*,3*R*,4*R*)-*t*-butyl 4-(3-amino-4-carbamoyl-1*H*-pyrazol-1-yl)-3-cyanocyclohexane-1-carboxylate (**Intermediate #47-4,** 11 g, 33 mmol), 1-bromo-4-chlorobenzene (9.2 g, 48 mmol), KOAc (9.4 g, 96 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.9 g, 5.0 mmol) and *t*-Butyl X-Phos (4.1 g, 10 mmol) in *iso*-propanol (100 mL) was degassed with bubbling N_2 gas for 15 minutes and then stirred at 85 °C under nitrogen for 16 hours, and then concentrated *in vacuo*. The crude residue was purified by MPLC on Silica gel (eluting with 1-2 % MeOH/DCM). Desired fractions were identified, combined, and concentrated *in vacuo*. The residue was further purified by reverse-phase preparative HPLC (using a gradient elution of 40-60 % MeCN /water with 0.5 % ammonia in 20) to afford the title compound. ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (s, 1H), 7.54 (d, *J* = 9.2 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 4.32 – 4.30 (m, 1H), 3.49 – 3.42 (m, 1H), 2.51 – 2.47 (m, 2H), 2.20 – 2.13 (m, 3H), 1.95 – 1.82 (m, 1H), 1.66 – 1.59 (m, 1H), 1.50 (s, 9H). MS ESI: $[M+H]^+$ *m/z* 444.



Step B: **(1S,3S,4S and 1R,3R,4R)-4-(4-Carbamoyl-3-((4-chlorophenyl)amino)-1*H*-pyrazol-1-yl)-3-cyanocyclohexanecarboxylic acid**

To a solution of (1*S*,3*S*,4*S* and 1*R*,3*R*,4*R*)-*t*-butyl 4-[4-carbamoyl-3-[(4-chlorophenyl)amino]-1*H*-pyrazol-1-yl]-3-cyanocyclohexane-1-carboxylate (500 mg, 1.1 mmol) in DCM (4 mL) was added TFA (2 mL) at 0 °C. The resulting solution was stirred at ambient temperature for 16 hours and then concentrated *in vacuo* to afford the title compound as an off-white solid, which was used directly without further purification. ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (s, 1H), 7.58 – 7.53 (m, 2H), 7.26 – 7.21 (m, 2H), 4.32 – 4.30 (m, 1H), 3.50 – 3.46 (m, 1H), 2.58 – 2.48 (m, 2H), 2.33 – 2.15 (m, 3H), 1.98 – 1.88 (m, 1H), 1.77 – 1.64 (m, 1H). MS ESI: $[M+H]^+$ *m/z* 388.

Step C: **3-((4-Chlorophenyl)amino)-1-((1S,2S,4S or 1R,2R,4R)-2-cyano-4-(3,3-dimethylazetidine-1-carbonyl)cyclohexyl)-1*H*-pyrazole-4-carboxamide**

To a solution of the crude acid (1*S*,3*S*,4*S* and 1*R*,3*R*,4*R*)-4-[4-carbamoyl-3-[(4-chlorophenyl)amino]-1*H*-pyrazol-1-yl]-3-cyanocyclohexane 1-carboxylic acid (200 mg, 0.5 mmol) in DMF (4 mL) were sequentially added 3,3-dimethylazetidin-1-ium chloride (75 mg, 0.62 mmol), EDC (120 mg, 0.62 mmol), HOBt (83 mg, 0.61 mmol) and triethylamine (120 mg, 1.2 mmol). The resulting solution was stirred at ambient temperature for 16 hours before it was concentrated *in vacuo*. The crude residue was partitioned between DCM (10 mL) and water (2 mL). The organic solution was washed with saturated aqueous $NaHCO_3$ (2x2 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by MPLC on Silica gel (eluting with 2-5 % MeOH/DCM) to afford a racemic mixture of 3-(4-chlorophenylamino)-1-((1*S*,2*S*,4*S* and 1*R*,2*R*,4*R*)-2-cyano-4-(3,3-dimethylazetidine-1-carbonyl)cyclohexyl)-1*H*-pyrazole-4-carboxamide, which was then resolved to the constituent enantiomers by preparative chiral HPLC (Chiralpak IC, 2*25cm; Mobile phase: 30 % ethanol (0.2 % DEA) /hexane (0.1 % DEA)] to afford the title compounds as single enantiomers.

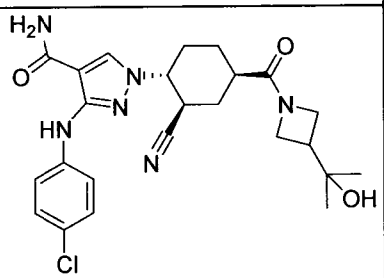
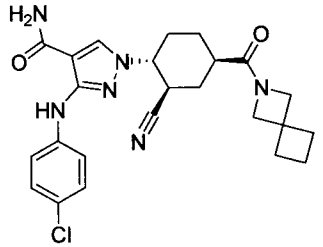
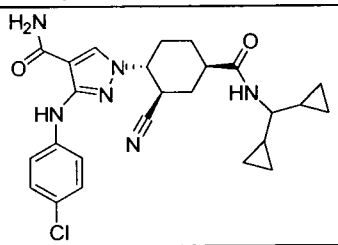
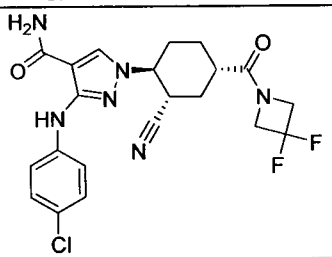
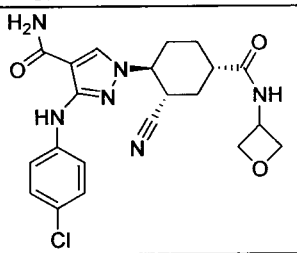
Example #35-1: 1st enantiomer to elute; 3-(4-chlorophenylamino)-1-((1*S*,2*S*,4*S* or 1*R*,2*R*,4*R*)-2-cyano-4-(3,3-dimethylazetidine-1-carbonyl)cyclohexyl)-1*H*-pyrazole-4-carboxamide. ^{1}H NMR (300 MHz, CD_3OD) δ 8.02 (s, 1H), 7.54 (d, *J* = 9.0 Hz, 2H), 7.23 (d, *J* = 9.0 Hz, 2H), 4.34 – 4.27 (m, 1H), 4.02 – 3.94 (m, 2H), 3.67 (s, 2H), 3.48 – 3.43 (m, 1H), 2.58 – 2.53 (m, 1H), 2.29 – 2.12 (m, 3H), 2.01 – 1.97 (m, 2H), 1.71 – 1.67 (m, 1H), 1.30 (s, 6H). MS ESI: $[M+H]^+$ *m/z* 455.

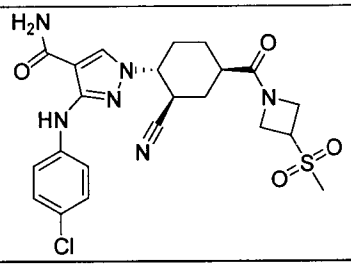
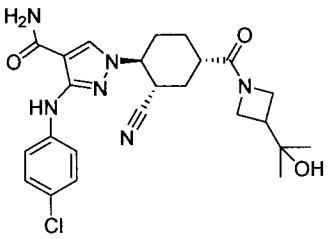
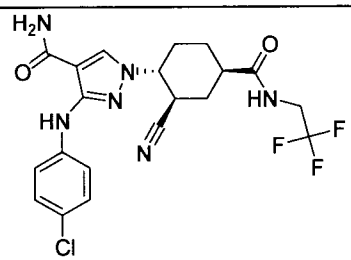
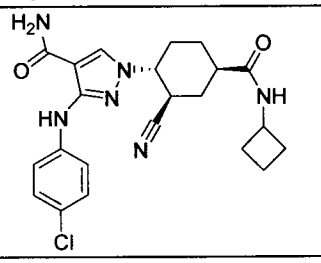
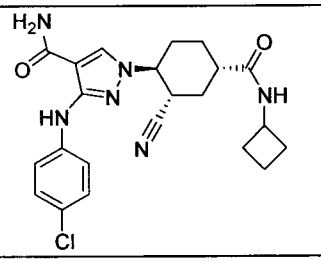
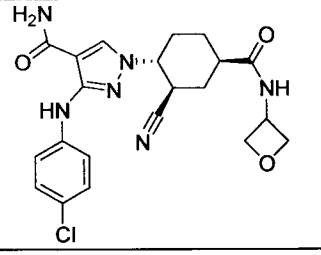
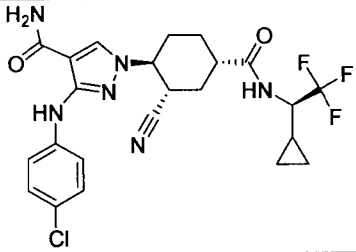
Example #35-2: 2nd enantiomer to elute; 3-(4-chlorophenylamino)-1-((1*R*,2*R*,4*R* or 1*S*,2*S*,4*S*)-2-cyano-4-(3,3-dimethylazetidine-1-carbonyl)cyclohexyl)-1*H*-pyrazole-4-carboxamide: ^{1}H NMR (300 MHz, CD_3OD) δ 8.02 (s, 1H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 9.0 Hz, 2H), 4.35 –4.28 (m, 1H), 4.04 – 3.96 (m, 2H), 3.68 (s, 2H), 3.54 – 3.45 (m, 1H), 2.59 – 2.54 (m, 1H), 2.30 – 2.14 (m, 3H), 2.03 – 1.94 (m, 2H), 1.72 – 1.68 (m, 1H), 1.30 (s, 6H). MS ESI: $[M+H]^+$ *m/z* 455.

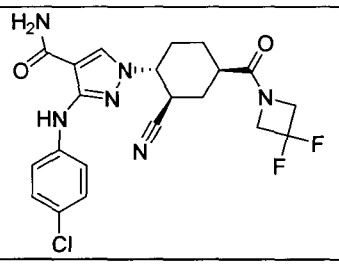
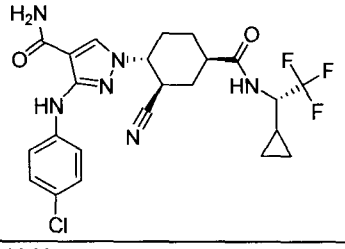
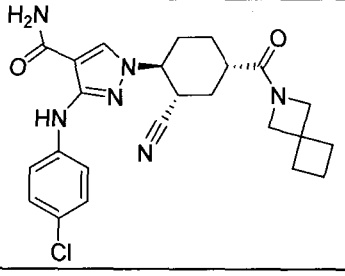
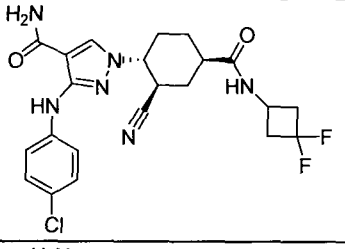
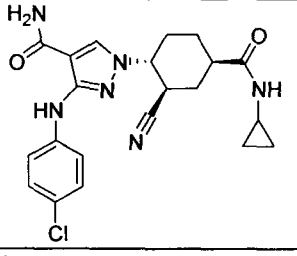
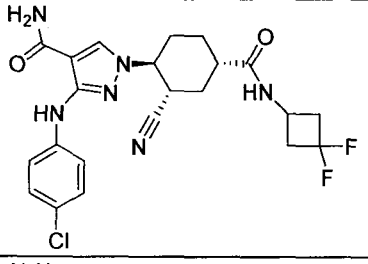
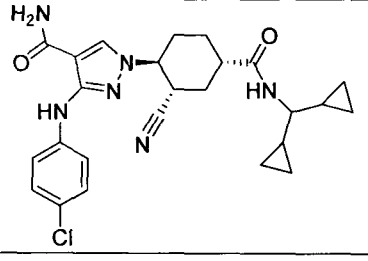
The following compounds shown in **TABLE 29** were prepared according to **Scheme #48** following similar procedures described for **Example #35-1** and **35-2**, which can be achieved by those of ordinary skill in the art of organic synthesis.

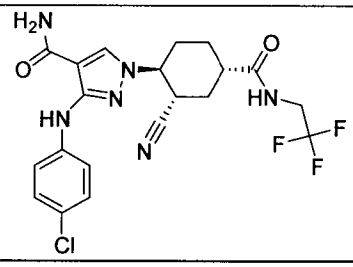
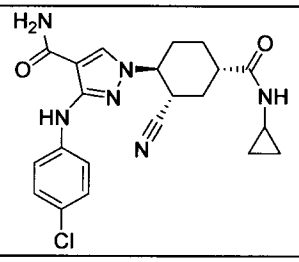
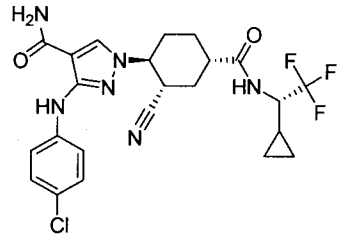
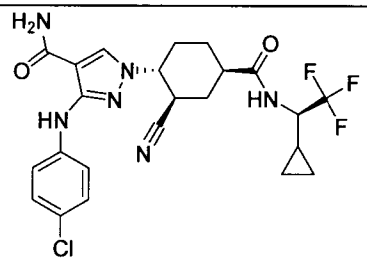
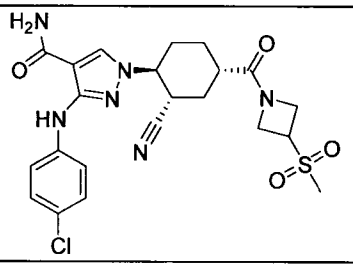
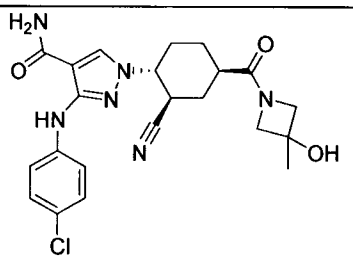
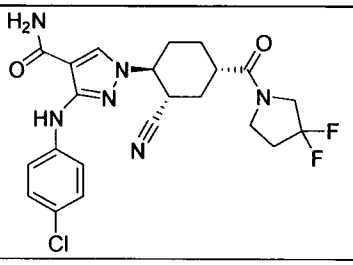
5

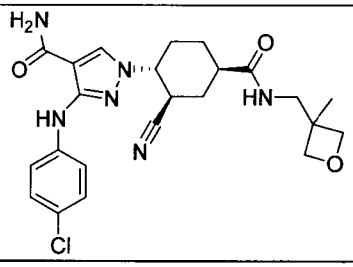
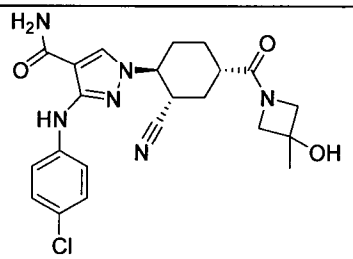
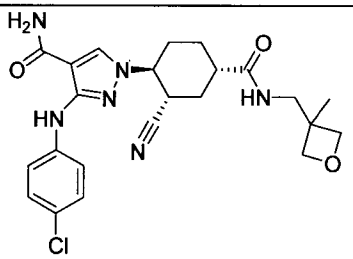
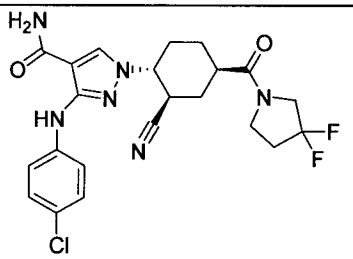
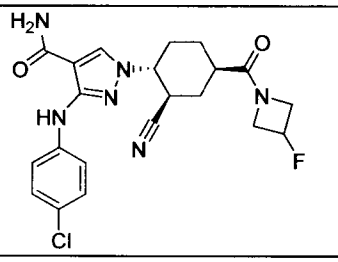
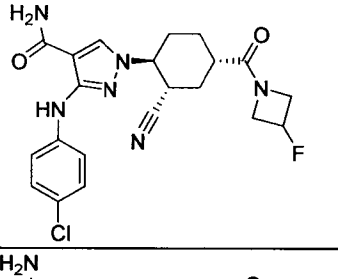
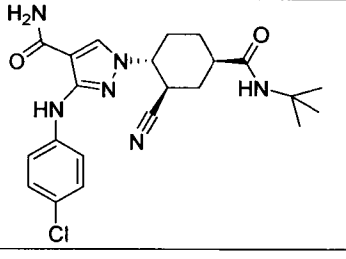
TABLE 29:

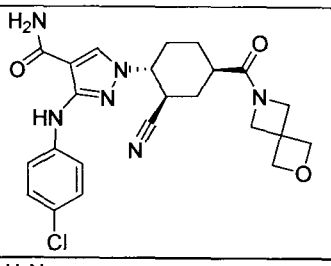
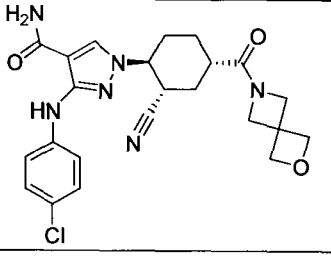
Example	Structure	Compound Name	Exact Mass [M+H]+
35-3		3-[(4-chlorophenyl)amino]-1-[(1R,2R,4R or 1S,2S,4S)-2-cyano-4-{[3-(1-hydroxy-1-methylethyl)azetidin-1-yl]carbonyl}cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 485, found 485
35-4		1-[(1R,2R,4R or 1S,2S,4S)-4-(2-azaspiro[3.3]hept-2-ylcarbonyl)-2-cyanocyclohexyl]-3-[(4-chlorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 467, found 467
35-5		3-[(4-chlorophenyl)amino]-1-{(1R,2R,4R or 1S,2S,4S)-2-cyano-4-[(dicyclopropylmethyl)carbamoyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 481, found 481
35-6		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(3,3-difluoroazetidin-1-yl)carbonyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 463, found 463
35-7		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(oxetan-3-ylcarbamoyl)cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 443, found 443

35-8		3-[(4-chlorophenyl)amino]-1-[(1R,2R,4R or 1S,2S,4S)-2-cyano-4-{[3-(methylsulfonyl)azetidin-1-yl]carbonyl}cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 505, found 505
35-9		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[3-(1-hydroxy-1-methylethyl)azetidin-1-yl]carbonyl}cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 485, found 485
35-10		3-[(4-chlorophenyl)amino]-1-{(1R,2R,4R or 1S,2S,4S)-2-cyano-4-[(2,2,2-trifluoroethyl)carbamoyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 469, found 469
35-11		3-[(4-chlorophenyl)amino]-1-[(1R,2R,4R or 1S,2S,4S)-2-cyano-4-(cyclobutylcarbamoyl)cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 441, found 441
35-12		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(cyclobutylcarbamoyl)cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 441, found 441
35-13		3-[(4-chlorophenyl)amino]-1-[(1R,2R,4R or 1S,2S,4S)-2-cyano-4-(oxetan-3-ylcarbamoyl)cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 443, found 443
35-14		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]carbamoyl}cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 509, found 509

35-15		3-[(4-chlorophenyl)amino]-1-{(1R,2R,4R or 1S,2S,4S)-2-cyano-4-[(3,3-difluoroazetidin-1-yl)carbonyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 463, found 463
35-16		3-[(4-chlorophenyl)amino]-1-[(1R,2R,4R or1S,2S,4S)-2-cyano-4-{[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]carbamoyl}cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 509, found 509
35-17		1-[(1S,2S,4S or 1R,2R,4R)-4-(2-azaspiro[3.3]hept-2-ylcarbonyl)-2-cyanocyclohexyl]-3-[(4-chlorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 467, found 467
35-18		3-[(4-chlorophenyl)amino]-1-{(1R,2R,4R or 1S,2S,4S)-2-cyano-4-[(3,3-difluorocyclobutyl)carbamoyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 477, found 477
35-19		3-[(4-chlorophenyl)amino]-1-[(1R,2R,4R or 1S,2S,4S)-2-cyano-4-(cyclopropylcarbamoyl)cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 427, found 427
35-20		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(3,3-difluorocyclobutyl)carbamoyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 477, found 477
35-21		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(dicyclopropylmethyl)carbamoyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 481, found 481

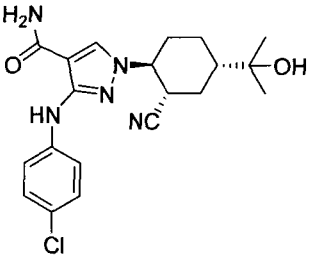
35-22		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(2,2,2-trifluoroethyl)carbamoyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 469, found 469
35-23		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(cyclopropylcarbamoyl)cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 427, found 427
35-24		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]carbamoyl}cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 509, found 509
35-25		3-[(4-chlorophenyl)amino]-1-[(1R,2R,4R or 1S,2S,4S)-2-cyano-4-{[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]carbamoyl}cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 509, found 509
35-26		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[3-(methylsulfonyl)azetidin-1-yl]carbonyl}cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 505, found 505
35-27		3-[(4-chlorophenyl)amino]-1-{(1R,2R,4R or 1S,2S,4S)-2-cyano-4-[(3-hydroxy-3-methylazetidin-1-yl)carbonyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 457, found 457
35-28		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(3,3-difluoropyrrolidin-1-yl)carbonyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 477, found 477

35-29		3-[(4-chlorophenyl)amino]-1-[(1R,2R,4R or 1S,2S,4S)-2-cyano-4-{[(3-methyloxetan-3-yl)methyl]carbamoyl}cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 471, found 471
35-30		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(3-hydroxy-3-methylazetidin-1-yl)carbonyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 457, found 457
35-31		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-{[(3-methyloxetan-3-yl)methyl]carbamoyl}cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 471, found 471
35-32		3-[(4-chlorophenyl)amino]-1-{(1R,2R,4R or 1S,2S,4S)-2-cyano-4-[(3,3-difluoropyrrolidin-1-yl)carbonyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 477, found 477
35-33		3-[(4-chlorophenyl)amino]-1-{(1R,2R,4R or 1S,2S,4S)-2-cyano-4-[(3-fluoroazetidin-1-yl)carbonyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 445, found 445
35-34		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4S or 1R,2R,4R)-2-cyano-4-[(3-fluoroazetidin-1-yl)carbonyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 445, found 445
35-35		1-[(1R,2R,4R or 1S,2S,4S)-4-(tert-butylcarbamoyl)-2-cyanocyclohexyl]-3-[(4-chlorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 443, found 443

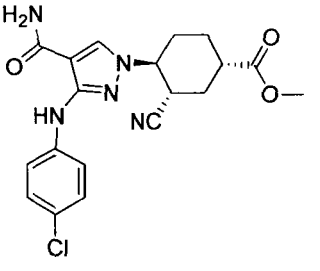
35-36		3-[(4-chlorophenyl)amino]-1-[(1R,2R,4R or 1S,2S,4S)-2-cyano-4-(2-oxa-6-azaspiro[3.3]hept-6-ylcarbonyl)cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 469, found 469
35-37		3-[(4-chlorophenyl)amino]-1-[(1S,2S,4S or 1R,2R,4R)-2-cyano-4-(2-oxa-6-azaspiro[3.3]hept-6-ylcarbonyl)cyclohexyl]-1*H*-pyrazole-4-carboxamide	Calc'd 469, found 469

Scheme #49

Example #36-1 and 36-2



3-(4-Chlorophenylamino)-1-((1*S*,2*S*,4*S* or 1*R*,2*R*,4*R*)-2-cyano-4-(2-hydroxypropan-2-yl)cyclohexyl)-1*H*-pyrazole-4-carboxamide



Step A: **(1S,3S,4S and 1R,3R,4R)-methyl 4-(4-carbamoyl-3-((4-chlorophenyl)amino)-1*H*-pyrazol-1-yl)-3-cyanocyclohexanecarboxylate**

To a solution of the crude acid (1*S*,3*S*,4*S* and 1*R*,3*R*,4*R*)-4-[4-carbamoyl-3-[(4-chlorophenyl)amino]-1*H*-pyrazol-1-yl]-3-cyanocyclohexane-1-carboxylic acid (**Example #35-1 Step C**, 500 mg, 1.3 mmol) in MeOH (5 mL) were sequentially added EDC (324 mg, 1.7 mmol) and HOBt (210 mg, 1.6 mmol). The resulting solution was stirred at ambient temperature overnight before it was concentrated *in vacuo*. The crude residue was partitioned between DCM (20 mL) and water (5 mL). The organic solution was washed with saturated aqueous $NaHCO_3$ (2x5 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by MPLC on Silica gel (eluting with 2-4 % MeOH/DCM) to afford the title compound. ^1H NMR (400 MHz, CD_3OD) δ 8.13 (s, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.24 (d, J =

9.2 Hz, 2H), 4.35 – 4.28 (m, 1H), 3.74 (s, 3H), 3.52 – 3.34 (m, 1H), 2.68 – 2.62 (m, 1H), 2.55 – 2.52 (m, 1H), 2.24 – 2.16 (m, 3H), 2.00 – 1.90 (m, 1H), 1.73 – 1.70 (m, 1H). MS ESI: $[M+H]^+$ *m/z* 401.

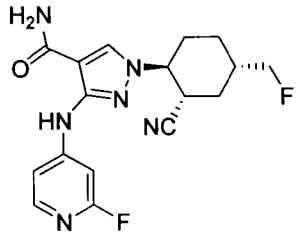
Step B: **3-(4-Chlorophenylamino)-1-((1*S*,2*S*,4*S* or 1*R*,2*R*,4*R*)-2-cyano-4-(2-hydroxypropan-2-yl)cyclohexyl)-1*H*-pyrazole-4-carboxamide**

To a solution of methyl (1*S*,3*S*,4*S* and 1*R*,3*R*,4*R*)-4-[4-carbamoyl-3-[(4-chlorophenyl)amino]-1*H*-pyrazol-1-yl]-3-cyanocyclohexane-1-carboxylate (100 mg, 0.25 mmol) in THF (8 mL) under nitrogen was added MeMgBr (1.8 mL, 2.5 mmol, 1.4N in THF) dropwise at -15 °C. The resulting solution was stirred at ambient temperature for 3 hours before the addition of saturated aqueous NH_4Cl (10 mL) at 0 °C. The mixture was vigorously stirred at ambient temperature for 10 minutes, and then extracted with EtOAc (3x30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by MPLC on Silica gel (eluting with 2-5 % MeOH/DCM) to afford a racemic mixture of 3-(4-chlorophenylamino)-1-((1*S*,2*S*,4*S* and 1*R*,2*R*,4*R*)-2-cyano-4-(2-hydroxypropan-2-yl)cyclohexyl)-1*H*-pyrazole-4-carboxamide, which was then resolved to the constituent enantiomers by preparative chiral HPLC (Chiralpak IC, 2*25cm; Mobile phase: 30 % ethanol/hexane (0.1 % TEA)] to afford the title compounds as single enantiomers.

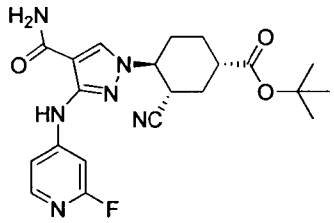
Example 36-1: 1st enantiomer to elute; 3-(4-chlorophenylamino)-1-((1*S*,2*S*,4*S* or 1*R*,2*R*,4*R*)-2-cyano-4-(2-hydroxypropan-2-yl)cyclohexyl)-1*H*-pyrazole-4-carboxamide: MS ESI: $[M+H]^+$ *m/z* 402.1; ^1H NMR (400 MHz, CD_3OD) δ 8.13 (s, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 4.28 – 4.22 (m, 1H), 3.39 – 3.35 (m, 1H), 2.44 – 2.41 (m, 1H), 2.19 – 2.03 (m, 3H), 1.70 – 1.59 (m, 2H), 1.56 – 1.45 (m, 1H), 1.22 (s, 6H).

Example 36-2: 2nd enantiomer to elute; 3-(4-chlorophenylamino)-1-((1*R*,2*R*,4*R* or 1*S*,2*S*,4*S*)-2-cyano-4-(2-hydroxypropan-2-yl)cyclohexyl)-1*H*-pyrazole-4-carboxamide: ^1H NMR (400 MHz, CD_3OD) δ 8.13 (s, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 4.28 – 4.22 (m, 1H), 3.39 – 3.32 (m, 1H), 2.44 – 2.41 (m, 1H), 2.19 – 2.03 (m, 3H), 1.70 – 1.57 (m, 2H), 1.54 – 1.45 (m, 1H), 1.23 (s, 6H). MS ESI : $[M+H]^+$ *m/z* 402.

Example #37

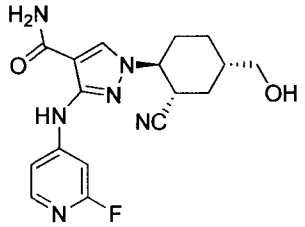


1-[(1*S*,2*S*,4*S* and 1R,2R,4R)-2-Cyano-4-(fluoromethyl)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide



Step A: **(1S,3S,4S and 1R,3R,4R)-tert-butyl 4-(4-carbamoyl-3-((2-fluoropyridin-4-yl)amino)-1*H*-pyrazol-1-yl)-3-cyanocyclohexanecarboxylate**

To a solution of *tert*-butyl (1S,3S,4S and 1R,3R,4R)-4-(3-amino-4-carbamoyl-1*H*-pyrazol-1-yl)-3-cyanocyclohexanecarboxylate (**Intermediate 47-4**, 409 mg, 1.23 mmol) in dioxane (10 mL) were added potassium acetate (781 mg, 3.68 mmol), 4-bromo-2-fluoropyridine (259 mg, 1.47 mmol), tetra methyl t-butyl X-Phos (118 mg, 0.245 mmol) and Pd_2dba_3 (112 mg, 0.123 mmol). The solution was degassed by bubbling argon, capped, and heated to 90 °C for 16 hours. The reaction mixture was cooled, filtered through celite, and purified by MPLC on silica gel (using a gradient elution of 0-100% EtOAc/hexanes) to the title compound. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.35 (broad s, 1H), 7.95 (d, *J* = 5.4 Hz, 1H), 7.70 (s, 1H), 7.29 (d, *J* = 1.2 Hz, 1H), 7.02 (d, *J* = 5.4 Hz, 1H), 5.50 (s, 1H), 4.02-3.98 (td, *J* = 11.4, 4.8 Hz, 1H), 3.26-3.22 (m, 1H), 2.58-2.40 (m, 2H), 2.30-2.14 (m, 3H), 1.92-84 (m, 1H), 1.59 (m, 1H), 1.45 (s, 9H). LRMS (ESI) calc'd for $C_{21}H_{26}FN_6O_3$ $[M+H]^+$: 429, Found: 429.



Step B: **1-((1S,2S,4S and 1R,2R,4R)-2-Cyano-4-(hydroxymethyl)cyclohexyl)-3-((2-fluoropyridin-4-yl)amino)-1*H*-pyrazole-4-carboxamide**

To a solution of 1S,3S,4S and 1R,3R,4R)-4-{4-carbamoyl-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexanecarboxylate (174 mg, 0.406 mmol) in THF (4 mL) was added lithium borohydride (27 mg, 1.2 mmol) and heated to 55 °C for 3 hours. After 3 hours, another 1 eq. of lithium borohydride (27 mg, 1.2 mmol) was added and the reaction mixture was stirred for another 1 hour. The reaction mixture was cooled, filtered through celite, and purified by MPLC on silica gel (using a gradient elution of 0-20% MeOH/DCM) to afford the title compound. LRMS (ESI) calc'd for $C_{17}H_{20}FN_6O_2$ $[M+H]^+$: 359, Found: 359.

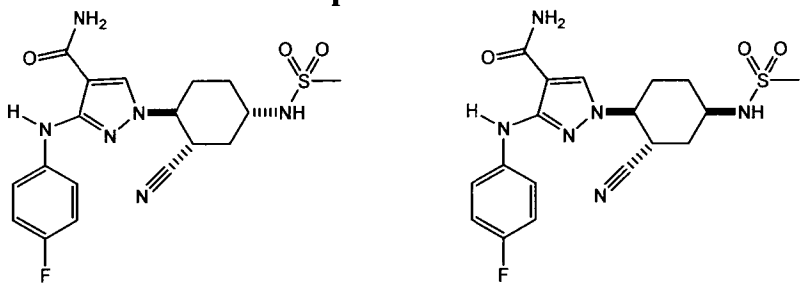
Step C: **1-[(1S,2S,4S and 1R,2R,4R)-2-Cyano-4-(fluoromethyl)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide**

To a solution of 1-[(1S,2S,4S and 1R,2R,4R)-2-cyano-4-(hydroxymethyl)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide (121 mg, 0.338 mmol) in DCM (2 mL) was added Dexo-Fluor (112 mg, 0.093 mmol). The resulting

solution was stirred for 16 hours and then concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 0-100% EtOAc/hexanes) to afford the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 8.20 (s, 1H), 7.90 (d, J = 5.5 Hz, 1H), 7.41 (s, 1H), 7.24 (d, J = 5 Hz, 1H), 4.42-4.20 (m, 3H), 3.49 (m, 1H), 2.35-2.32 (m, 1H), 2.59-2.08 (m, 2H), 1.97-1.85 (m 2H), 1.69-1.64 (m, 1H), 1.47 (1.38 (m, 1H). LRMS (ESI) calc'd for $C_{17}H_{19}F_2N_6O$ $[M+H]^+$: 361, Found: 361.

Scheme #35

Example #38-1 & 38-2



1-{(1S,2S,4S and 1R,2R,4R)-2-Cyano-4-[(methylsulfonyl)amino]cyclohexyl}-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide and **1-{(1S,2S,4R and 1R,2R,4S)-2-Cyano-4-[(methylsulfonyl)amino]cyclohexyl}-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide**

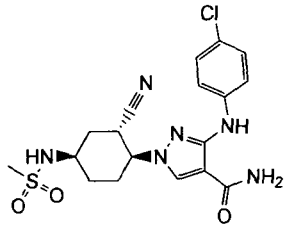
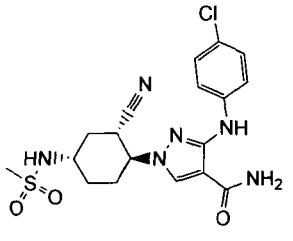
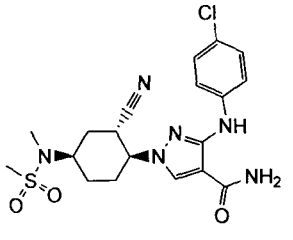
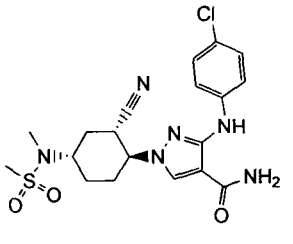
To a suspension of (3S,4S and 3R,4R)-4-(4-carbamoyl-3-((4-fluorophenyl)amino)-1*H*-pyrazol-1-yl)-3-cyanocyclohexanaminium trifluoroacetate (**Example #27-18**, 34 mg, 0.074 mmol) in DCM (0.37 mL) was added TEA (0.03 mL, 0.2 mmol), followed by methanesulfonyl chloride (0.006 mL, 0.07 mmol). The resulting mixture was allowed to stir at ambient temperature for 1 hour before saturated aqueous $NaHCO_3$ was added and the resulting mixture was extracted with EtOAc (3x). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 0–10%, MeOH/DCM). Desired fractions were identified, combined, and concentrated *in vacuo*. The major isomer was further purified by reverse-phase preparative HPLC (using a gradient elution of MeCN/water, with 0.1% v/v TFA modifier). Desired fractions were identified, combined, basified with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*, to afford the title compounds.

Example 38-1 (Major isomer:): 1-{(1S,2S,4S and 1R,2R,4R)-2-cyano-4-[(methylsulfonyl)amino]cyclohexyl}-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide ^{1}H NMR (500 MHz, CD_3OD) δ 8.10 (s, 1H), 7.53 (m, 2H), 6.98 (m, 2H), 4.27 (ddd, J = 11.5, 11.5, 3.5 Hz, 2H), 3.57-3.44 (m, 2H), 3.01 (s, 3H), 2.53 (m, 1H), 2.09 (m, 3H), 1.79 (ddd, J = 12.5, 12.5, 12.5 Hz, 1H), 1.57, (dddd, J = 13.5, 13.5, 13.5, 4 Hz, 1H). LRMS (ESI) calc'd for $C_{18}H_{21}FN_6O_3S$ $[M+H]^+$: 421, Found: 421.

Example 38-2 (Minor isomer): 1-{(1S,2S,4R and 1R,2R,4S)-2-cyano-4-[(methylsulfonyl)amino]cyclohexyl}-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide. ^{1}H NMR (500 MHz, CD_3OD) δ 8.13 (s, 1H), 7.54 (m, 2H), 6.99 (m, 2H), 4.32 (ddd, *J* = 11, 11, 3.5 Hz, 1H), 3.79 (m, 1H), 3.66 (ddd, *J* = 11.5, 11.5, 3 Hz, 1H), 3.01 (s, 3H), 2.43-2.32 (m, 2H), 2.12-1.84 (m, 4H). LRMS (ESI) calc'd for $C_{18}H_{21}FN_6O_3S$ $[M+H]^+$: 421, Found: 421.

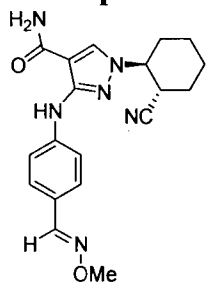
The following compounds shown in **TABLE 30** were prepared according to **Scheme #35** following similar procedures described for **Example #38-1 and 38-2**, which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 30:

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
38-3		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4R and 1R,2R,4S)-2-cyano-4-[(methylsulfonyl)amino]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 437, found 437
38-4		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4R and 1R,2R,4S)-2-cyano-4-[(methylsulfonyl)amino]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 437, found 437
38-5		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4R and 1R,2R,4S)-2-cyano-4-[methyl(methylsulfonyl)amino]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 451, found 451
38-6		3-[(4-chlorophenyl)amino]-1-{(1S,2S,4R and 1R,2R,4S)-2-cyano-4-[methyl(methylsulfonyl)amino]cyclohexyl}-1*H*-pyrazole-4-carboxamide	Calc'd 451, found 451

Scheme #55

Example #39

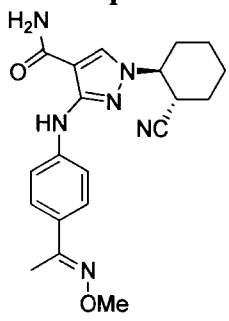


1-[(1S,2S or 1R, 2R)-2-Cyanocyclohexyl]-3-({4-[(methoxyimino)methyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide

To a solution of 1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-[(4-formylphenyl)amino]-1*H*-pyrazole-4-carboxamide (20 mg, 0.059 mmol) in EtOH (0.5 mL) were added O-methylhydroxylamine hydrochloride (25 mg, 0.30 mmol) and triethylamine (30 mg, 0.29 mmol). The vial was sealed and heated in the microwave at 100 °C for 30 minutes. The reaction mixture was filtered and purified directly by reverse phase preparative HPLC (using a gradient elution of 10-100% MeCN water). Desired fractions were identified, combined, and concentrated *in vacuo* to afford the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 8.11 (s, 1H), 8.00 (s, 1H), 7.56 (d, J = 9 Hz, 2H), 7.50 (d, J = 9 Hz, 2H), 4.28-4.21 (td, J = 11, 4.5 Hz, 1H), 3.86 (s, 3H), 3.31-3.30 (m, 1H), 2.29-2.26 (m, 1H), 2.07-1.74 (m, 5H), 1.53-1.41 (m, 2H). LRMS (ESI) calc'd for $C_{19}H_{23}N_6O_2$ $[M+H]^+$: 367, Found: 367.

Scheme #55

Example #40

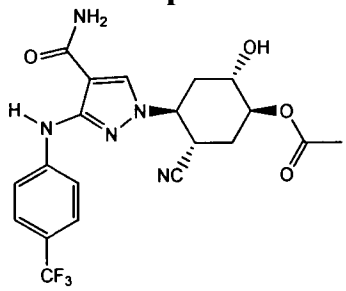


1-[(1S,2S or 1R,2R)-2-Cyanocyclohexyl]-3-{[4-(N-methoxyethanimidoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide

1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-{[4-(N-methoxyethanimidoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide was prepared using the same procedure described for the preparation of as 1-[(1S,2S or 1R, 2R)-2-cyanocyclohexyl]-3-({4-[(methoxyimino)methyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide (**Example #39**). ^{1}H NMR (500 MHz, CD_3OD): δ 8.11 (s, 1H), 7.58 (d, J = 9 Hz, 2H), 7.54 (d, J = 9 Hz, 2H), 4.28-4.21 (td, J = 11, 4 Hz, 1H), 3.92 (s, 3H), 3.31-3.30 (m, 1H), 2.31-2.26 (m, 1H), 2.18 (s, 3H), 2.1-1.70 (m, 5H) 1.58-1.40 (m, 2H). LRMS (ESI) calc'd for $C_{20}H_{25}N_6O_2$ $[M+H]^+$: 381, Found: 381.

Scheme #46

Example #41



Step A-C: (1S,2S,4S,5S and 1R,2R,4R,5R)-4-(4-Carbamoyl-3-((4-(trifluoromethyl)phenyl)amino)-1*H*-pyrazol-1-yl)-5-cyano-2-hydroxycyclohexyl acetate

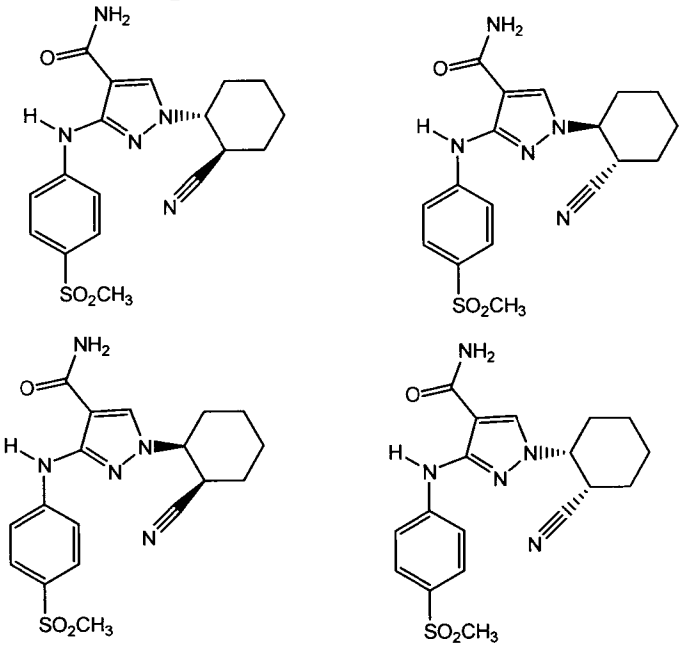
BAST (0.47 mL, 2.5 mmol) was added to a mixture of 1-((1S,2S,4R)-2-cyano-4-hydroxycyclohexyl)-3-((4-(trifluoromethyl)phenyl)amino)-1*H*-pyrazole-4-carboxamide (**Intermediate A of Example #28-1**, 0.50 g, 1.3 mmol) in DCM (25.4 mL) at 23 °C. 20 minutes after the addition of BAST, the reaction mixture was partitioned between EtOAc and saturated aqueous sodium bicarbonate solution. The organic layer was washed with brine, and the washed solution was dried over anhydrous sodium sulfate. The dried solution was filtered, and the filtrate was concentrated *in vacuo* to afford a mixture of olefin isomers and a fluorinated product. The crude reaction product was dissolved in EtOAc (12.7 mL) and *m*-CPBA (77% by weight, 854 mg, 3.81 mmol) was added. The reaction mixture was stirred at 23 °C for 17 hours, and then aqueous sodium bisulfite solution (40% by weight) was added. The biphasic mixture was stirred for 15 minutes, then was partitioned between EtOAc and water. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate solution and brine, and the washed solution was dried over anhydrous sodium sulfate. The dried solution was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by MPLC on silica gel (using a gradient elution of 50-100% EtOAc/hexanes) to afford an epoxide product of undetermined stereochemistry. The epoxide product (80 mg, 0.20 mmol) was dissolved in acetic acid and heated to 70 °C. After stirring for 4 hours at 70 °C, the reaction mixture was cooled to 23 °C and partitioned between EtOAc and saturated aqueous sodium bicarbonate solution. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by reverse-phase preparative HPLC (using a gradient elution of

MeCN/water, with 0.1% v/v TFA modifier). Desired fractions were identified, combined, neutralized with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title compound. ^1H NMR (500 MHz, DMSO-d_6): δ 9.49 (s, 1H), 8.34 (s, 1H), 7.70–7.86 (m, 3H), 7.57 (d, J = 8.5 Hz, 2H), 7.27 (br s, 1H), 4.79–4.77 (m, 1H), 4.59 (td, J = 11.5, 4.0 Hz, 1H), 3.92–3.88 (m, 1H), 3.47 (td, J = 12.0, 4.0 Hz, 1H), 2.29–2.17 (m, 3H), 2.11 (s, 3H), 1.97 (td, J = 13.5, 3.4 Hz, 1H). LRMS (ESI) calc'd for $C_{20}H_{21}F_3N_5O_4$ $[M+H]^+$: 452, Found: 452.

CHIRAL RESOLUTION

The following experimental procedures exemplify the chiral resolution and isolation of enantiopure Examples of the instant invention. The following Examples are for illustrative purposes only and are not intended to limit the scope of the instant invention in any way.

Examples #42-1, 42-2, 42-3, and 42-4



1-[(1S,2S or 1R,2R)-2-Cyanocyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide *and* 1-[(1S,2R or 1R,2S)-2-cyanocyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide

A racemic diastereomeric mixture of 1-(2-cyanocyclohexyl)-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide was chirally resolved to the four constituent enantiomers by SFC chromatography (Chiral Technology AD-H 2.1x25cm, 5uM, 30% EtOH/CO2). Desired fractions were identified, combined, and concentrated *in vacuo* to afford enantiomerically pure samples of the title compounds:

Example 42-1: 1st eluting stereoisomer, 1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide

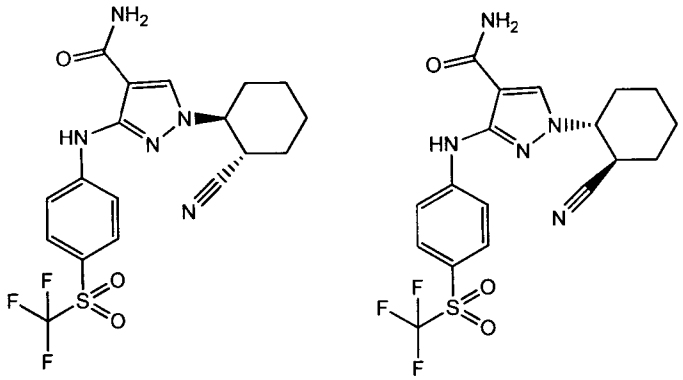
1HNMR (600 MHz, CDCl3): δ 9.32 (s, 1H), 7.81 (d, J = 9.0 Hz, 2H), 7.78 (s, 1H), 7.66 (d, J = 9.0 Hz, 2H), 5.80 (s, 2H), 4.03-3.98 (m, 1H), 3.20-3.15 (m, 1H), 3.03 (s, 3H) 2.32 (br d, J = 13.8 Hz, 1H), 2.12-2.06 (m, 2H), 1.96 (br d, J = 12.9 Hz, 1H), 1.90-1.86 (m, 1H), 1.76-1.69 (m, 1H), 1.48-1.38 (m, 2H). LRMS (ESI) calc'd for $C_{18}H_{22}N_5O_3S$ [M+H]+: 388, Found: 388.

Example 42-2: 2nd eluting stereoisomer, 1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide ^{1}H NMR spectral data is consistent with the data reported for **Example #42-1**. LRMS (ESI) calc'd for C18H22N5O3S [M+H]+: 388, Found: 388.

Example 42-3: 3rd eluting stereoisomer, 1-[(1S,2R or 1R,2S)-2-cyanocyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide
1HNMR (600 MHz, CDCl3): δ 9.29 (s, 1H), 7.82-7.78 (m, 3H), 7.67 (d, J = 8.4 Hz, 2H), 5.69 (s, 2H), 4.29 (dt J = 12.0, 3.9 Hz, 1H,), 3.71-68 (m, 1H), 3.03 (s, 3H), 2.24-2.19 (m, 2H), 2.15-2.06 (m, 2H), 1.86-1.79 (m, 2H), 1.74-1.65 (m, 1H), 1.56-1.48 (m, 1H). LRMS (ESI) calc'd for C18H22N5O3S [M+H]+: 388, Found: 388.

Example 42-4: 4th eluting stereoisomer, 1-[(1S,2R or 1R,2S)-2-cyanocyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide ^{1}H NMR spectral data is consistent with the data reported for **Example #42-3**. LRMS (ESI) calc'd for C18H22N5O3S [M+H]+: 388, Found: 388.

Examples #43-1 and 43-2



1-[(1*S*,2*S* or 1*R*,2*R*)-2-Cyanocyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide

1-[(1*S*,2*S* and 1*R*,2*R*)-2-Cyanocyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl] phenyl}amino)-1*H*-pyrazole-4-carboxamide was chirally resolved to the two constituent enantiomers by chiral SFC (Chiral Technology IC-H, 2.1x25 cm, 35% MeO*H*-CO_2, 100 mL/minutes, 35 °C, 100 bar). Desired fractions were identified, combined, and concentrated *in vacuo* to afford enantiomerically pure samples of the title compounds:

Example 43-1: First-eluting enantiomer, 1-[(1*S*,2*S* or 1*R*,2*R*)-2-cyanocyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide.

^{1}*H*-NMR data is consistent with spectral data reported for the racemic mixture, **Example #16**. LRMS (ESI) calc'd for $C_{18}H_{19}F_3N_5O_3S$ $[M+H]^+$: 442, Found: 442.

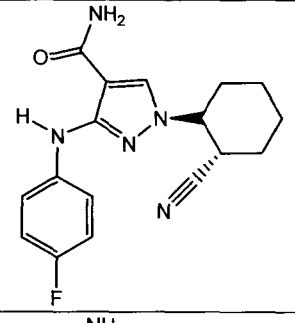
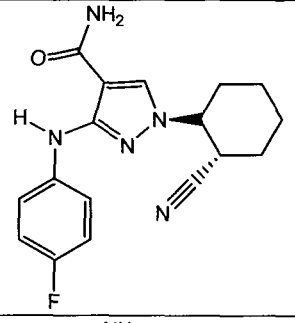
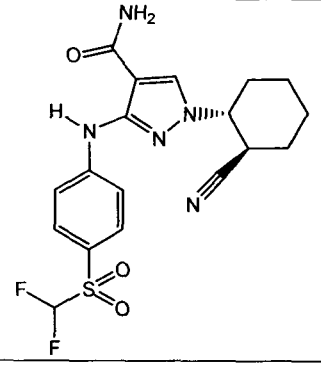
Example 43-2: Second-eluting enantiomer, 1-[(1*S*,2*S* or 1*R*,2*R*)-2-cyanocyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide.

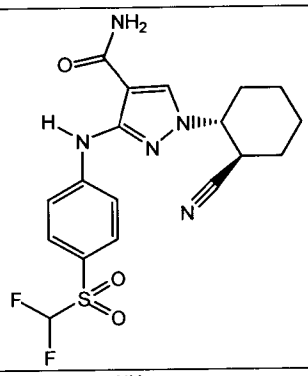
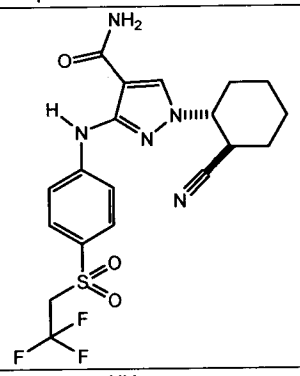
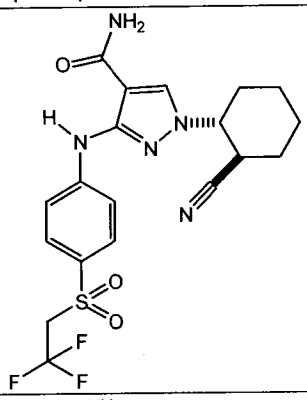
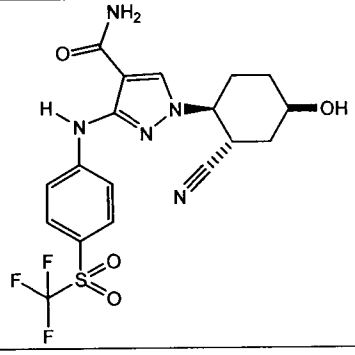
^{1}*H*-NMR data is consistent with spectral data reported for the racemic mixture, **Example #16.**

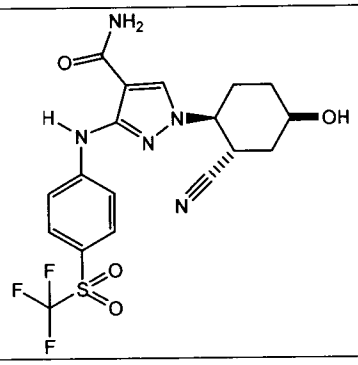
LRMS (ESI) calc'd for $C_{18}H_{19}F_3N_5O_3S$ $[M+H]^+$: 442, Found: 442.

The following compounds shown **TABLE 31** were prepared following similar procedures described for **Examples #42-1 and 42-2**, which can be achieved by those of ordinary skill in the art of organic synthesis.

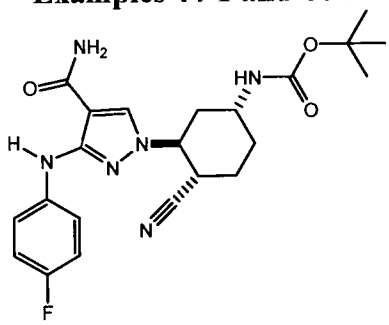
TABLE 31:

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
43-3		1-[(1S,2R or 1R,2S)-2-cyanocyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 328, Found 328
43-4		1-[(1R,2S or 1S,2R)-2-cyanocyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide	Calc'd 328, Found 328
43-5		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-({4-[(difluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 424, Found 424

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
43-6		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-({4-[(difluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 424, Found 424
43-7		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-({4-[(2,2,2-trifluoroethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 456, Found 456
43-8		1-[(1S,2S or 1R,2R)-2-cyanocyclohexyl]-3-({4-[(2,2,2-trifluoroethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 456, Found 456
43-9		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 458, Found 458

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
43-10		1-[(1S,2S,4R or 1R,2R,4S)-2-cyano-4-hydroxycyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide	Calc'd 458, Found 458

Examples 44-1 and 44-2



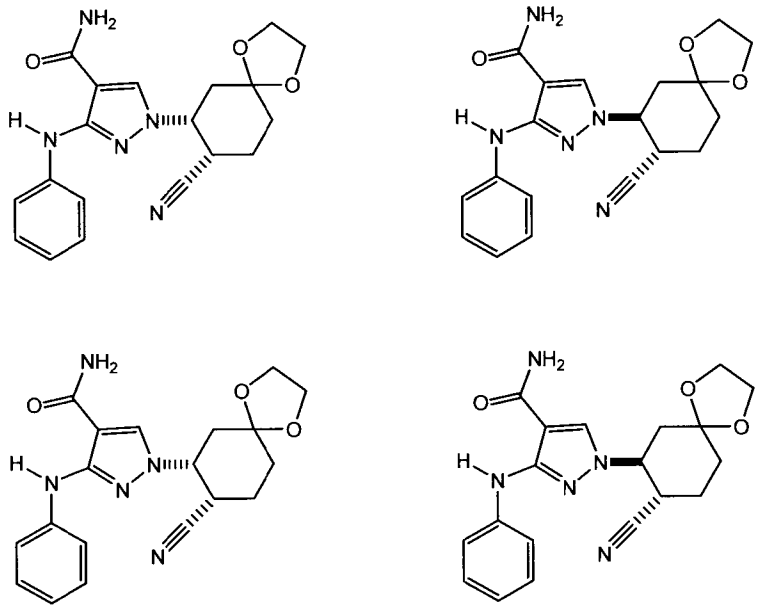
tert-Butyl [(1R,3S,4S or 1S,3R,4R)- 3-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-4-cyanocyclohexyl]carbamate

tert-Butyl [(1R,3S,4S and 1S,3R,4R)- 3-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-4-cyanocyclohexyl]carbamate was chirally resolved to the constituent enantiomers by chiral SFC (Chiral Technology OD-H, 2.1x25 cm, 25% MeOH/CO_2, 60 mL/minutes). Desired fractions were identified, combined, and concentrated *in vacuo* to afford enantiomerically pure samples of the title compounds:

Example 44-1: 1 *tert*-Butyl [(1R,3S,4S or 1S,3R,4R)- 3-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-4-cyanocyclohexyl]carbamate, first enantiomer to elute from column. LRMS (ESI) calc'd for $[M+H]^+$: 443, Found: 443.

Example 44-2: *tert*-Butyl [(1R,3S,4S or 1S,3R,4R)- 3-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-4-cyanocyclohexyl]carbamate, second enantiomer to elute from column. LRMS (ESI) calc'd for $[M+H]^+$: 443, Found: 443.

Examples #45-1, 45-2, 45-3, and 45-4



1-[(7R,8S or 7S,8R)- 8-Cyano-1,4-dioxaspiro[4.5]dec-7-yl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide *and* 1-[(7S,8S or 7R,8R)- 8-Cyano-1,4-dioxaspiro[4.5]dec-7-yl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide

A racemic diastereomeric mixture of 1-(8-cyano-1,4-dioxaspiro[4.5]dec-7-yl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide was chirally resolved to the four constituent enantiomers by SFC chromatography (Chiral Technology AS-H 2.1 X 25cm, 5uM, 30% MeOH/CO_2). Desired fractions were identified, combined, and concentrated *in vacuo* to afford enantiomerically pure samples of the title compounds:

Example 45-1: 1st enantiomer to elute from column; 1-[(7R,8R or 7S,8S)-8-Cyano-1,4-dioxaspiro[4.5]dec-7-yl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide.. ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.06 (s, 1H), 8.31 (s, 1H), 7.58-7.48 (m, 3H), 7.20 (t, *J* = 7.9 Hz, 2H), 7.12 (br s, 1H), 6.79 (t, *J* = 7.3 Hz, 1H), 4.38 (dt, *J* = 12.9, 3.9 Hz, 1H), 4.00–3.86 (m, 4H), 3.79–3.75 (m, 1H), 2.29–2.24 (m, 1H), 2.09 (t, *J* = 12.8 Hz, 1H), 2.04–1.99 (m, 1H), 1.90 (tt, *J* = 14.1, 3.8 Hz, 1H), 1.79–1.74 (m, 1H), 1.66 (td, *J* = 13.9, 4.3 Hz, 1H). LRMS (ESI) calc'd for $C_{19}H_{21}N_5O_3$ [M+H]+: 368, Found: 368.

Example 45-2: 2nd enantiomer to elute from column; 1-[(7S,8R or 7R,8S)-8-Cyano-1,4-dioxaspiro[4.5]dec-7-yl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide. ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.11 (s, 1H), 8.24 (s, 1H), 7.60 (br s, 1H), 7.47 (d, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 7.9 Hz, 2H), 7.14 (br s, 1H), 6.80 (t, *J* = 7.3 Hz, 1H), 4.34 (td, *J* = 11.5, 4.4 Hz, 1H), 3.97–3.83 (m, 4H), 3.37 (td, *J* = 12.0, 3.7 Hz, 1H), 2.19–2.03 (m, 3H), 1.83–1.64 (m, 3H). LRMS (ESI) calc'd for $C_{19}H_{21}N_5O_3$ [M+H]+: 368, Found: 368.

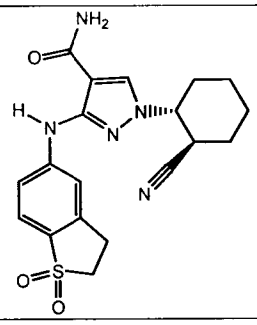
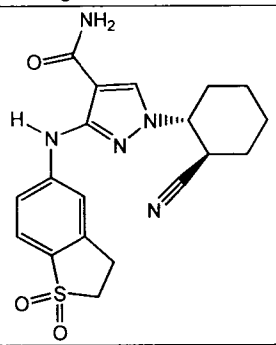
Example 45-3: 3rd enantiomer to elute from column ; 1-[(7R,8R or 7S,8S)-8-Cyano-1,4-dioxaspiro[4.5]dec-7-yl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide. ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.06 (s, 1H), 8.31 (s, 1H), 7.58-7.48 (m, 3H), 7.20 (t, *J* = 7.9 Hz, 2H), 7.12 (br s, 1H), 6.79 (t, *J* = 7.3 Hz, 1H), 4.38 (dt, *J* = 12.9, 3.9 Hz, 1H), 4.00–3.86 (m, 4H), 3.79–3.75 (m,

1H), 2.29–2.24 (m, 1H), 2.09 (t, J = 12.8 Hz, 1H), 2.04–1.99 (m, 1H), 1.90 (tt, J = 14.1, 3.8 Hz, 1H), 1.79–1.74 (m, 1H), 1.66 (td, J = 13.9, 4.3 Hz, 1H). LRMS (ESI) calc'd for $C_{19}H_{21}N_5O_3$ [M+H]+: 368, Found: 368.

Example 45-4: 4th enantiomer to elute from column; 1-[(7S,8R or 7R,8S)-8-Cyano-1,4-dioxaspiro[4.5]dec-7-yl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide. ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.11 (s, 1H), 8.24 (s, 1H), 7.60 (br s, 1H), 7.47 (d, J = 7.7 Hz, 2H), 7.22 (t, J = 7.9 Hz, 2H), 7.14 (br s, 1H), 6.80 (t, J = 7.3 Hz, 1H), 4.34 (td, J = 11.5, 4.4 Hz, 1H), 3.96–3.83 (m, 4H), 3.37 (td, J = 12.1, 3.8 Hz, 1H), 2.21–2.01 (m, 3H), 1.84–1.63 (m, 3H). LRMS (ESI) calc'd for $C_{19}H_{21}N_5O_3$ [M+H]+: 368, Found: 368.

The following examples shown in **TABLE 33** were prepared following similar procedures described for **Examples #45-1, 45-2, 45-3, and 45-4**, which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 33:

Example	Structure	Compound Name	Exact Mass $[M+H]^+$
45-5		**1-[(1S,2R or 1R,2S)-2-cyanocyclohexyl]-3-[(1,1-dioxido-2,3-dihydro-1-benzothiophen-5-yl)amino]-1*H*-pyrazole-4-carboxamide**	**Calc'd 400, Found 400**
45-6		**1-[(1S,2R or 1R,2S)-2-cyanocyclohexyl]-3-[(1,1-dioxido-2,3-dihydro-1-benzothiophen-5-yl)amino]-1*H*-pyrazole-4-carboxamide**	**Calc'd 400, Found 400**

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 ambient 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 ambient 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 ambient 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. The following table tabulates the biological data disclosed for the instant invention as JAK1 IC_{50} and JAK2 IC_{50} values.

Example	JAK1 IC_{50}	JAK2 IC_{50}
1-1	96	696
1-2	8	101
1-3	24	138
1-4	0.5	11
1-5	5	82
2-1	3	36
2-2	6	70
2-3	9	47
2-4	423	>1500
2-5	700	>1500
2-6	370	1000
2-7	170	320
2-8	174	635
2-9	16	202
2-10	13	100
2-11	5	49
2-12	15	79
2-13	27	185
2-14	2	18
2-15	0.6	9
3-1	6	109
3-2	2	49
4	5	46
5	2	13
6-1	410	>1500
6-2	305	>1500
6-3	250	>1500
6-4	4	55
6-5	410	>1500
6-6	11	170
7-1	17	464

Example	JAK1 IC_{50}	JAK2 IC_{50}
7-2	14	101
8	2	22
9	12	247
10	11	357
11-1	54	176
11-2	11	50
11-3	2	49
11-4	0.8	20
11-5	0.8	22
11-6	7	38
11-7	5	19
11-8	158	>1500
11-9	21	434
11-10	110	1300
12-1	7	50
12-2	257	>1500
13-1	0.34	5
13-2	0.62	9
14	0.32	3
15	3	46
16	2	17
17-1	2	21
17-2	23	436
17-3	19	123
17-4	0.58	7
17-5	1	9
17-6	4	25
17-7	4	31
17-8	2	10
17-9	0.5	5
17-10	0.35	4
17-11	2	8
17-12	0.49	5
17-13	10	36
17-14	83	226

Example	JAK1 IC_{50}	JAK2 IC_{50}
17-15	20	76
17-16	11	36
17-17	1	5
17-18	3	22
17-19	3	18
17-20	0.17	0.79
17-21	1	4
17-22	3	60
17-23	11	55
17-24	33	75
17-25	0.53	3
17-26	1	11
17-27	0.30	2
17-28	3	30
17-29	0.36	3
17-30	0.10	1
17-31	0.60	10
17-32	2	11
17-33	2	4
17-34	2	11
17-35	3	15
17-36	0.19	2
17-37	0.67	3
17-38	1	4
17-39	1	3
17-40	0.24	5
17-41	2	16
17-42	18	178
17-43	0.12	7
17-44	3	18
17-45	3	10
17-46	0.35	3
17-47	7	39
17-48	2	14
17-49	17	93

Example	JAK1 IC_{50}	JAK2 IC_{50}
17-50	0.20	2
17-51	7	42
17-52	2	26
17-52	1	72
17-53	3	28
17-54	18	119
17-55	41	255
17-56	4	37
17-57	0.20	0.66
17-58	6	42
17-59	2	13
17-60	6	23
17-61	4	21
17-62	0.28	2
17-63	0.45	11
17-64	2	14
17-65	0.16	2
17-66	0.33	1
17-67	3	9
17-68	0.40	1
17-69	30	67
17-70	3	13
17-71	60	285
17-72	12	89
17-73	16	37
17-74	12	49
17-75	6	22
17-76	0.55	7
17-77	4	18
17-78	6	17
17-79	7	40
17-80	12	26
17-81	0.35	2
17-82	0.50	1
17-83	0.20	0.90

Example	JAK1 IC_{50}	JAK2 IC_{50}
17-84	0.30	1
17-85	0.90	4
17-86	0.25	0.95
17-87	0.50	2
17-88	1	9
17-89	0.50	1
17-90	1	4
17-91	0.50	2
17-92	0.90	3
17-93	0.30	1
17-94	5	33
17-95	6	31
17-96	2	7
17-97	9	24
17-98	0.25	1
17-99	0.40	1
17-100	4	34
17-101	2	9
17-102	6	39
17-103	0.70	5
17-104	2	25
17-105	2	19
17-106	1	10
17-107	0.95	11
17-108	8	120
17-109	50	260
18	10	22
19-1	3	8
19-2	4	11
20	0.40	6
21-1	6	73
21-2	2	15
21-3	2	16
22-1	4	28
22-2	4	30

Example	JAK1 IC_{50}	JAK2 IC_{50}
23-1	5	60
23-2	67	212
24	6	61
25-1	8	84
25-2	2	17
25-3	1	26
25-4	0.55	3
25-5	1	10
25-6	3	20
25-8	0.60	4
25-9	1	6
25-10	4	17
25-11	0.45	2
25-12	3	20
25-13	0.25	3
25-14	6	25
25-15	0.30	3
25-16	3	10
25-17	0.35	2
25-20	1	4
25-21	1	11
25-22	3	49
25-23	2	28
25-24	1	8
25-25	15	210
25-26	0.60	8
25-27	0.55	11
25-28	0.10	3
25-29	2	26
26-1	2	9
26-2	6	76
26-3	69	150
26-4	21	74
26-5	2	14
26-6	1	32

Example	JAK1 IC_{50}	JAK2 IC_{50}
26-7	0.90	9
26-8	1	19
26-9	4	33
26-10	21	102
26-11	350	>1500
27-1	0.20	5
27-2	0.5	12
27-3	0.80	25
27-4	1	56
27-5	0.20	11
27-6	0.08	5
27-7	0.40	9
27-8	0.30	9
27-9	3	51
27-10	0.70	7
27-11	0.55	6
27-12	0.30	10
27-13	0.30	6
27-14	0.25	11
27-15	0.35	11
27-16	1	35
28-1	0.40	23
28-2	4	67
28-3	5	87
28-4	0.75	39
28-5	1	18
28-6	0.55	16
28-7	0.40	49
28-8	5	200
28-9	2	84
28-10	3	64
28-11	6	75
28-12	380	>1500
28-13	11	175
28-14	7	100

Example	JAK1 IC_{50}	JAK2 IC_{50}
28-15	0.90	22
28-16	1	21
28-17	2	121
28-18	30	400
28-19	31	675
28-20	5	355
28-21	3	335
28-22	8	145
28-23	0.45	23
28-24	0.60	240
28-25	8	155
28-26	0.40	35
28-27	50	800
28-28	3	77
28-30	15	575
28-31	105	1100
28-32	5	144
28-33	8	180
28-34	0.60	20
28-35	1	48
28-36	2	84
28-37	2	120
28-38	7	173
28-39	2	35
28-40	0.70	16
28-41	2	58
28-42	2	36
28-43	2	26
28-44	0.06	11
28-45	0.20	24
28-47	0.30	11
28-48	8	215
28-49	0.15	5
28-50	2	47
28-51	0/20	37

Example	JAK1 IC_{50}	JAK2 IC_{50}
28-52	0.40	23
28-53	0.40	8
28-54	5	92
28-55	4	200
28-57	0.15	8
28-58	0.70	23
28-60	0.20	9
28-61	0.06	4
28-62	0.15	12
28-63	4	41
28-65	0.30	12
28-66	0.45	16
28-68	0.06	1
28-69	0.60	16
28-70	2	40
28-71	2	97
28-72	0.45	98
28-75	0.25	80
28-76	0.04	2
28-77	0.70	4
28-78	0.20	7
28-79	0.30	3
28-80	0.30	130
28-81	0.20	24
28-83	0.40	18
28-84	0.30	9
28-85	0.65	17
28-86	0.75	18
28-87	0.55	13
28-88	0.10	7
28-89	0.30	6
28-90	4	35
28-91	1	65
28-92	0.10	27
28-93	0.06	5

Example	JAK1 IC_{50}	JAK2 IC_{50}
28-94	2	44
28-95	1	32
28-96	2	85
28-97	0.30	9
28-98	4	216
28-99	3	32
28-100	0.70	41
28-101	4	69
28-102	1	27
28-103	6	147
28-104	0.40	13
28-105	3	30
28-106	9	53
28-107	2	31
28-108	2	31
28-109	2	110
28-110	2	37
28-111	1	16
28-112	0.45	6
28-113	1	13
28-114	3	29
28-115	3	33
28-116	1	9
28-117	0.55	23
28-118	0.50	17
28-119	1	85
28-120	0.95	20
28-121	1	61
28-122	0.90	6
28-123	2	56
28-124	1	23
28-125	2	72
28-126	0.50	5
28-127	12	254
28-128	3	110

Example	JAK1 IC_{50}	JAK2 IC_{50}
28-129	20	620
28-130	0.25	5
28-131	0.90	51
28-133	0.50	36
28-134	1	50
28-135	0.65	32
28-136	1	61
28-137	0.90	22
28-138	0.90	40
28-139	5	113
28-141	1	44
28-142	2	141
28-143	1	122
28-144	1	21
28-145	0.25	15
28-146	1	4
28-147	0.45	5
28-148	0.35	4
28-149	0.60	17
28-150	0.30	2
28-151	0.13	1
28-152	0.40	10
28-153	0.40	7
28-154	1	13
28-155	0.22	3
28-156	1	14
28-157	1	28
28-158	1	17
28-159	2	18
28-160	0.20	1
28-164	4	225
28-165	0.45	4
28-166	2	55
28-167	3	82
28-168	0.15	4

Example	JAK1 IC_{50}	JAK2 IC_{50}
28-169	0.29	5
28-170	11	180
28-171	2	31
28-172	0.20	8
28-173	0.15	24
28-174	0.15	8
28-175	0.35	19
28-176	0.20	11
28-177	1	43
28-178	0.15	2
28-179	7	170
28-180	0.60	39
28-181	1	16
28-182	0.15	12
28-183	0.80	61
28-184	0.20	23
28-185	0.80	83
28-186	0.15	9
28-187	0.20	25
28-188	0.30	14
28-189	0.35	21
28-190	2	270
28-191	0.90	104
28-192	2	67
28-193	165	1000
28-194	4	152
28-195	177	375
28-196	1	34
28-197	7	430
28-198	0.15	3
28-199	0.30	9
28-200	1	23
28-201	2	62
28-202	0.75	39
28-203	2	285

Example	JAK1 IC_{50}	JAK2 IC_{50}
28-204	0.20	26
28-205	0.90	21
28-206	12	195
28-207	1	22
28-208	0.15	17
28-209	3	208
28-210	1	41
28-211	4	71
28-212	0.60	36
28-213	1	12
28-214	1	38
28-215	0.80	28
28-216	2	24
28-217	2	47
28-218	4	102
28-219	1	11
28-220	2	30
28-221	2	42
28-222	0.80	43
28-223	2	14
28-224	3	34
28-225	12	51
28-226	5	36
28-227	27	186
28-228	2	48
28-229	1	38
28-230	4	24
28-231	16	170
28-232	0.65	7
28-233	1	6
28-234	2	63
28-235	0.85	25
28-236	0.90	23
28-237	1	33
28-238	2	38

Example	JAK1 IC_{50}	JAK2 IC_{50}
28-239	2	20
28-240	2	27
28-241	2	28
29	1	35
30-1	9	106
30-2	4	135
30-4	1	265
30-5	21	665
30-6	125	1500
30-7	6	420
30-8	6	240
30-9	16	910
30-10	10	610
30-12	40	1200
30-13	11	500
30-14	51	1050
30-15	260	>1500
30-16	2	242
30-17	0.85	17
30-18	2	136
31-1	0.30	33
31-2	1	35
31-3	1	28
31-4	1	34
31-5	0.85	28
32-1	13	59
32-2	1	4
32-3	0.70	3
32-4	0.35	2
32-5	3	25
32-6	2	5
32-7	5	28
32-8	0.75	4
32-9	1	4
32-10	1	9

Example	JAK1 IC_{50}	JAK2 IC_{50}
32-11	1	4
32-12	1	10
32-13	3	17
32-14	15	73
32-15	0.25	1
32-16	0.85	6
32-17	2	11
33-1	0.50	5
33-2	0.25	6
33-3	2	12
33-4	5	90
33-5	0.25	2
33-6	0.50	3
33-7	11	75
33-8	8	33
33-9	21	65
33-10	0.30	2
33-11	0.45	3
33-12	0.45	2
33-13	0.20	0.95
33-14	4	14
33-15	0.50	2
33-16	0.70	3
33-18	3	10
33-19	1	4
33-20	2	20
33-21	1	6
33-22	2	17
34-1	7	107
34-2	5	164
34-3	0.95	13
34-4	2	19
34-5	7	88
34-6	1	12
34-7	0.85	9

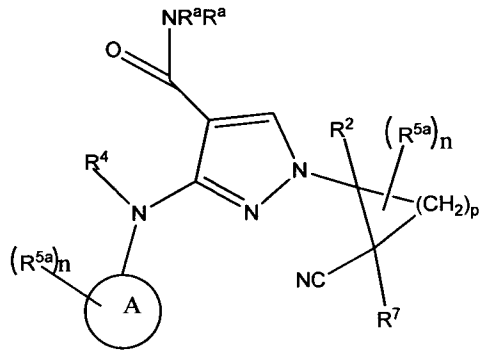
Example	JAK1 IC_{50}	JAK2 IC_{50}
34-8	6	94
34-9	3	51
35-1	6	45
35-2	9	290
35-3	9	59
35-4	16	133
35-5	13	169
35-6	62	>500
35-7	33	243
35-8	3	19
35-9	30	315
35-10	3	38
35-11	10	78
35-12	20	103
35-13	5	38
35-14	9	>500
35-15	3	28
35-16	9	58
35-17	66	480
35-18	13	136
35-19	5	23
35-20	21	172
35-21	25	500
35-22	7	218
35-23	37	295
35-24	180	>500
35-25	21	306
35-26	2	49
35-27	5	35
35-28	3	115
35-29	38	>500
35-30	10	180
35-31	9	59
35-32	5	60
35-33	9	200

Example	JAK1 IC_{50}	JAK2 IC_{50}
35-34	3	23
35-35	47	425
35-36	10	111
35-37	43	>500
36-1	0.65	4
36-2	3	20
37	0.80	13
38-1	2	14
38-2	0.90	12
38-3	0.90	8
38-4	0.50	5
38-5	12	46
38-6	1	6
39	0.45	2
40	0.35	2
41	20	184
42-1	0.25	3
42-2	3	27
42-3	32	85
42-4	2	7
43-1	16	119
43-2	1	9
43-3	16	150
43-4	2	15
43-5	3	28
43-6	0.30	2
43-7	2	18
43-8	0.15	1
43-9	2	31
43-10	0.20	3
44-1	2	43
44-2	30	990
44-3	5	72
44-4	30	1000
44-5	3	46

Example	JAK1 IC_{50}	JAK2 IC_{50}
44-6	11	200
44-7	1	29
45-1	44	235
45-2	0.85	4
45-3	147	308
45-4	13	59
45-6	2	32
45-7	0.25	4

CLAIMS

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



I

$\mathbf{R^a}$ and $\mathbf{R^4}$ are each independently selected from hydrogen and C_1-$_4$alkyl;

A is selected from aryl, and heteroaryl;

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

p is 2, 3, or 4;

$\mathbf{R^2}$ and $\mathbf{R^7}$ are each independently selected from

hydrogen,

halogen,

C_{1-10} alkyl,

C_{2-10} alkenyl,

C_{1-10} heteroalkyl,

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

C_{3-8} cycloalkylC_{0-10} alkyl,

heteroaryl C_{0-10} alkyl,

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

and wherein each of $\mathbf{R^2}$ and $\mathbf{R^7}$ are independently substituted with 0, 1, 2, 3, or 4 $\mathbf{R^{5a}}$ substituents;

$\mathbf{R^{5a}}$ 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,

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,

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

aryl C_{2-10} alkynyl(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_{1-10} heteroalkyl(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,
(C_{0-10})heteroalkylaminocarbonyloxy,
aryl (C_{0-10})alkylaminocarbonyloxy,
(C_{3-8})cycloalkyl(C_{0-10})alkylaminocarbonyloxy,
heteroaryl(C_{0-10})alkylaminocarbonyloxy,
(C_{3-8})heterocycloalkyl(C_{0-10})alkylaminocarbonyloxy,
C_{0-10} alkylamino(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{2-10}$ alkenyl,
C_{1-10} alkylamino(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,
(C_{0-10})heteroalkylamin(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,
C_{3-8} cycloalkyl C_{0-10} alkylamino(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,
aryl C_{0-10}alkylamino(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,
heteroarylC_{0-10}alkylamino((oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,
(C_{3-8})heterocycloalkylC_{0-10}alkylamino(oxy)$_{0-1}$(carbonyl)$_{0-1}C_{0-10}$ alkyl,
C_{1-10} 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} alkyl (oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
aryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
(C_{3-8})heterocycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
-CO_2(C_{0-10} alkyl),
-(C_{0-10} alkyl)CO_2H,
Oxo (=O),
formyl,
sulfonyl,
C_{1-10} alkylsulfonyl,
C_{1-10} heteroalkylsulfonyl,

(C_{3-8}) cycloalkylsulfonyl,
(C_{3-8}) cycloheteroalkylsulfonyl,
heteroarylsulfonyl,
arylsulfonyl,
aminosulfonyl,
$-SO_2N(C_{0-6}alkyl)_{1-2}$,
$-SO_2C_{1-6}alkyl$,
$-SO_2CF_3$,
$-SO_2CF_2H$,
$-Si(CH_3)_3$
C_{1-10} alkylsulfinyl,
amino,
$(C_{0-10}$ alkyl$)_{1-2}$ amino,
C_{1-4}acylamino C_{0-10} alkyl,
hydroxyl,
$(C_{1-10}$ alkyl$)OH$,
C_{0-10} alkylalkoxyl,
$imino(C_{0-10}alkyl)$,
$(C_{0-10}alkyl)imino$,
cyano,
C_{1-6}alkylcyano, and
C_{1-6}haloalkyl;

wherein two $\mathbf{R^{5a}}$ and the atom to which they are attached may optionally form a 3-, 4-, 5-, or 6- membered saturated ring system;

wherein $\mathbf{R^{5a}}$ is each optionally substituted with 1, 2, 3, or 4 $\mathbf{R^6}$ substituents and $\mathbf{R^6}$ 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,
aryl C_{2-10} alkenyl$(oxy)_{0-1}(carbonyl)_{0-1}C_{0-10}$ alkyl,
aryl C_{2-10} alkynyl$(oxy)_{0-1}(carbonyl)_{0-1}C_{0-10}$ 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,
(C_{3-8})cycloalkyl(C_{0-10})alkylaminocarbonyloxy,
heteroaryl(C_{0-10})alkylaminocarbonyloxy,
(C_{3-8})heterocycloalkyl(C_{0-10})alkylaminocarbonyloxy,
C_{1-10} alkylamino(oxy)$_{0-1}$carbonylC_{0-10} alkyl,
C_{3-8} cycloalkyl C_{0-10} alkylamino(oxy)$_{0-1}$carbonylC_{0-10} alkyl,
aryl C_{0-10} alkylamino(oxy)$_{0-1}$carbonylC_{0-10} alkyl,
heteroaryl C_{0-10} alkylamino(oxy)$_{0-1}$carbonylC_{0-10} alkyl,
(C_{3-8})heterocycloalkyl C_{0-10} alkylamino(oxy)$_{0-1}$carbonylC_{0-10} alkyl,
C_{1-10} alkyl (oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
C_{3-8} cycloalkyl C_{0-10} alkyl (oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
aryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
heteroaryl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
(C_{3-8})heterocycloalkyl C_{0-10} alkyl(oxy)$_{0-1}$(carbonyl)$_{0-1}$aminoC_{0-10} alkyl,
-CO_2(C_{0-10} alkyl),
-(C_{0-10} alkyl)CO_2H,
Oxo (=O),
Sulfonyl,
C_{1-10} alkylsulfonyl,
C_{1-10} heteroalkylsulfonyl,
(C_{3-8})cycloalkylsulfonyl,
(C_{3-8})cycloheteroalkylsulfonyl,
heteroarylsulfonyl,
arylsulfonyl,
aminosulfonyl,
-SO_2N(C_{1-6}alkyl)$_{1-2}$,
-SO_2C_{1-6}alkyl,
-SO_2CF_3,
-SO_2CF_2H,
C_{1-10} alkylsulfinyl,

-OSi(C_{1-10} alkyl)$_3$,
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,
imino(C_{0-10}alkyl),
(C_{0-10}alkyl)imino,
hydroxy,
(C_{1-10} alkyl)OH,
C_{1-10} alkoxy,
cyano, and
C_{1-6}haloalkyl;

wherein two $\mathbf{R^6}$ and the atoms to which they are attached may optionally form a 3-, 4-, 5-, or 6- membered saturated ring system; and

$\mathbf{R^6}$ 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, C_{1-10} heteroalkylsulfonyl, oxo (O=), (C_{3-8}) cycloalkylsulfonyl, (C_{3-8}) cycloheteroalkylsulfonyl, heteroarylsulfonyl, arylsulfonyl, aminosulfonyl, -SO_2N(C_{1-6}alkyl)$_{1-2}$, -SO_2C_{1-6}alkyl, -SO_2CF_3, -SO_2CF_2H, -C_{1-10} alkylsulfinyl, -OSi(C_{1-10}alkyl)$_3$, -O$_{(0-1)}$(C_{1-10})haloalkyl, amino(C_{1-6}alkyl)$_{0-2}$ and NH_2; with the proviso that the compound of formula I is other than:

1-[(1R,2S,6S and 1S,2R,6R)-2-cyano-6-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-[(1S,2R and 1R,2S)-2-cyanocyclohexyl]-3-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1*H*-pyrazole-4-carboxamide; and

3-[(2-chloropyridin-4-yl)amino]-1-[(1S,2R and 1R,2S)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide.

2. . A compound of or a pharmaceutically acceptable salt or a stereoisomer thereof is selected from:

1-[2-cyanocyclopentyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyanocyclopentyl}-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-{[2-cyanocyclopentyl]}-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyanocyclopentyl]}-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-((2-cyanocyclohexyl)-3-(phenylamino)-1H-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-(8-cyano-1,4-dioxaspiro[4.5]dec-7-yl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
methyl-3-[4-carbamoyl-3-(phenylamino)-1*H*-pyrazol-1-yl]-4-cyanocyclohexanecarboxylate;
1-[2-cyano-6-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-3-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-5-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
[4-({4-Carbamoyl-1-[2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]acetic acid;
[4-({4-carbamoyl-1-[2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]acetic acid;
1-[2-Cyano-4-hydroxycyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-Cyano-4-hydroxycyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-5-(dimethylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-5-(dimethylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;
1-{[2-cyano-5-(methylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;
1-{[5-(benzylamino)-2-cyanocyclohexyl}-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;
tert-Butyl-4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexanecarboxylate;
methyl-4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3- cyanocyclohexanecarboxylate;
1-2-Cyano-4-(hydroxymethyl)cyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide;
1-((4-(Aminomethyl)-2-cyanocyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide;
1-((2-Cyano-4-formylcyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide;
1-{2-Cyano-5,5-dimethylcyclohexyl}-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
tert-butyl [3-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-4-cyanocyclohexyl]carbamate;
1-(2-cyano-5-methylcyclohexyl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-(5-cyanospiro[2.5]octan-6-yl)-3-((2-fluoropyridin-4-yl)amino)-1*H*-pyrazole-4-carboxamide;
tert-butyl {[3-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-4-cyanocyclohexyl]methyl}carbamate;
tert-butyl {[3-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-4-cyanocyclohexyl]methyl}carbamate;
tert-butyl 3-(4-carbamoyl-3-(phenylamino)-1H-pyrazol-1-yl)-4-cyanocyclohexanecarboxylate;
1-[2-Cyano-4-hydroxycyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-Cyano-4-hydroxycyclohexyl]-3-({4-[(difluoromethyl) sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-Cyano-4-hydroxycyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[(2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

tert-butyl 4-[4-carbamoyl-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazol-1-yl]-3-cyanocyclohexanecarboxylate;

1-[2-Cyanocyclohexyl]-3-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-Cyanocyclohexyl]-3-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(methylcarbamoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-cyanophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(2-chloropyridin-4-yl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[3-fluoro-4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(difluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[(2-cyanocyclohexyl]-3-{[4-(ethylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(2,2,2-trifluoroethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(methylcarbamoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-cyanophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({3-(hydroxymethyl)-4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(6-fluoropyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[1-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-isoindol-5-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[1-oxo-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-isoindol-5-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[2-(1-methyl-1*H*-pyrazol-4-yl)pyridin-4-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(6-fluoropyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-formylphenyl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-bromophenyl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-acetylphenyl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[3,3,3-trifluoro-2-hydroxy-1,1-dimethylpropyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[3,3,3-trifluoro-2-hydroxy-1,1-dimethylpropyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({3-fluoro-4-[3,3,3-trifluoro-2-hydroxy-1,1-dimethylpropyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({6-[2,2,2-trifluoro-1-hydroxy-1-methylethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({6-[2,2-difluoro-1-hydroxyethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({6-[2,2-difluoro-1-hydroxy-1-methylethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(7-fluoroquinolin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(6-chloropyridin-3-yl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

2-[4-({4-carbamoyl-1-[2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]-2-methylpropanoic acid;

3-[(6-chloropyridin-3-yl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(6-chloropyridin-3-yl)amino]-1-[(1R,2R)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(6-chloropyridin-3-yl)amino]-1-[(1S,2S)-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-{[4-(aminomethyl)phenyl]amino}-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({6-[2,2,2-trifluoro-1-hydroxyethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide;

3-[(5-chloropyridin-3-yl)amino]-1-[(2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(6-fluoroquinolin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[(2-cyanocyclohexyl]-3-[(3,4-dichlorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({6-[2,2,2-trifluoro-1-hydroxyethyl]pyridin-3-yl}amino)-1*H*-pyrazole-4-carboxamide;

3-[(3-chloro-5-fluorophenyl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

2-[4-({4-carbamoyl-1-[2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)phenyl]-2-methylpropanoic acid;

1-[2-cyanocyclohexyl]-3-(pyridazin-4-ylamino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(3,5-dichlorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[6-(difluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(4-chloro-3-fluorophenyl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-{1,1-dimethyl-2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl}phenyl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(3-chloro-4-fluorophenyl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[6-(difluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(6-chloroquinolin-3-yl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;
3-[(7-chloroquinolin-3-yl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-[(3-hydroxy-1,1-dioxido-2,3-dihydro-1-benzothiophen-5-yl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-[(1,1-dioxido-1-benzothiophen-5-yl)amino]-1*H*-pyrazole-4-carboxamide;
1-[(2-cyanocyclohexyl]-3-({4-[(difluoromethyl)sulfonyl]-3-(hydroxymethyl)phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-({4-[(fluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-({4-[(cyclopropylmethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-{[4-(pyridin-2-ylsulfamoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-({4-[(2-morpholin-4-ylethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
3-({4-[(4-benzylpiperidin-1-yl)sulfonyl]phenyl}amino)-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;
methyl 5-({4-carbamoyl-1-[2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)pyridine-2-carboxylate;
N-tert-butyl-5-({4-carbamoyl-1-[2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)pyridine-3-carboxamide;
methyl 5-({4-carbamoyl-1-[2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)pyridine-3-carboxylate;
1-[2-cyanocyclohexyl]-3-[(5-methylpyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-[(5-cyanopyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-[(6-cyanopyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-[(7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-b]pyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-[(6-cyano-5-methylpyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;
methyl 5-({4-carbamoyl-1-[2-cyanocyclohexyl]-1*H*-pyrazol-3-yl}amino)-3-methylpyridine-2-carboxylate;
1-[2-cyanocyclohexyl]-3-[(6-cyano-5-fluoropyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-[(6-cyclopropylpyridin-3-yl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-{[4-(pyridin-4-ylsulfamoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-{[4-(cyclohexylsulfamoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
3-{[4-(benzylsulfamoyl)phenyl]amino}-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-({4-[(pyridin-3-ylmethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-({4-[(pyridin-2-ylmethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyanocyclohexyl]-3-({4-[(pyridin-4-ylmethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(2-pyrrolidin-1-ylethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(2,6-dimethylphenyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

3-({4-[(4-acetylpiperazin-1-yl)sulfonyl]phenyl}amino)-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-({4-[(4-chlorobenzyl)sulfamoyl]phenyl}amino)-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(1,4-dioxa-8-azaspiro[4.5]dec-8-ylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(1-methylethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(quinolin-7-ylsulfamoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-{[4-(trifluoromethyl)phenyl]sulfamoyl}phenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-{[4-(trifluoromethyl)benzyl]sulfamoyl}phenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-{[4-(3-methoxyphenyl)piperazin-1-yl]sulfonyl}phenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(2-methoxyethyl)sulfamoyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(morpholin-4-ylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(3,4-difluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(difluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-(2-Cyano-5-hydroxy-2-methylcyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-(2-cyano-5-fluoro-2-methylcyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-2-cyano-2-methylcyclohexyl)-3-((4-fluorophenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-[2-Cyanocyclohexyl]-3-[(1,1-dioxido-2,3-dihydro-1-benzothiophen-5-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[(2-Cyanocyclohexyl]-3-{[5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[(2-cyanocyclohexyl]-3-{[6-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-{[6-(1*H*-pyrazol-4-yl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-Cyano-4-fluorocyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-[6-cyanocyclohex-3-en-1-yl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-[2-Cyano-6-fluorocyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-(2-cyano-4(R)-hydroxycyclohexyl)-3-((4-(trifluoromethoxy)phenyl)amino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;
3-[(4-chloro-3-fluorophenyl)amino]-1-[2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-[(4-cyanophenyl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-[(3,4-dichlorophenyl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-({4-[(1S or 1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(2-fluoro-1,1-dimethylethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(1-methoxy-1-methylethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
3-[(6-chloropyridin-3-yl)amino]-1-[2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-[(4-cyclopropylphenyl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-{[6-(difluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-({4-[(1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(3-methyloxetan-3-yl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;
3-[(4-chlorophenyl)amino]-1-[2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-{[3-fluoro-4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(difluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
3-[(4-chlorophenyl)amino]-1-[2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-hydroxycyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;
1-[2-Cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-({4-[(1R or 1S)-2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(cyclopropylmethoxy)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;
1-[(4-[4-carbamoyl-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazol-1-yl]-3-cyano-N,N-dimethylcyclohexanaminium trifluoroacetate;
1-[2-cyano-4-(methylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(ethylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(methylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide,
1-[2-cyano-4-(dimethylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(cyclopropylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-{2-cyano-4-[(2,2,2-trifluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-{2-cyano-4-[(2,2,2-trifluoroethyl)amino]cyclohexyl}-3-({4-[(difluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(morpholin-4-yl)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide;
1-{(2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide;
1-{2-cyano-4-[(2-hydroxyethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide;
1-{2-cyano-4-[(2-methoxyethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide;
1-{2-cyano-4-[(2-fluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2-fluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl)amino)-1*H*-pyrazole-4-carboxamide;

1-[4-(Azetidin-1-yl)-2-cyanocyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-((4-(Azetidin-1-yl)-2-cyanocyclohexyl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-(4-(tert-butyl(methyl)amino)-2-cyanocyclohexyl)-3-((4-chlorophenyl)amino)-1H-pyrazole-4-carboxamide;

1-{2-cyano-4-[3-(1-hydroxy-1-methylethyl)azetidin-1-yl]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[1-cyclopropylethyl]amino}cyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2,4-dimethylazetidin-1-yl]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(cyclopropylmethyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(dimethylamino)cyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[(1S)-1-cyclopropylethyl]amino}cyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(dimethylamino)cyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[6-(hydroxymethyl)-3-azabicyclo[3.1.0]hex-3-yl]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[(3-methyloxetan-3-yl)methyl]amino}cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(dimethylamino)cyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[(1-hydroxycyclopropyl)methyl]amino}cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(4-chloro-3-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-chloro-3-fluorophenyl)amino]-1-2-cyano-4-(dimethylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chloro-3-fluorophenyl)amino]-1-[(2-cyano-4-(methylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(methylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
3-[(4-chloro-3-fluorophenyl)amino]-1-[2-cyano-4-{[1-cyclopropylethyl]amino}cyclohexyl]-1*H*-pyrazole-4-carboxamide;
1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-({4-[(1R)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[6-(difluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;
1-[4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[4-(tert-butylamino)-2-cyanocyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[4-(2,2,2-trifluoroethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(dimethylamino)cyclohexyl]-3-{[4-(trifluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-{[1-cyclopropylethyl]amino}cyclohexyl]-3-{[4-(trifluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[4-(trifluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide;
1-[4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
1-[2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;
3-[(3-chloro-4-fluorophenyl)amino]-1-{2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-1*H*-pyrazole-4-carboxamide;
1-[(4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(4-formylphenyl)amino]-1*H*-pyrazole-4-carboxamide;
3-[(4-chloro-3-fluorophenyl)amino]-1-[2-cyano-4-{[1-cyclopropylethyl]amino}cyclohexyl]-1*H*-pyrazole-4-carboxamide;
2-[4-({1-[(4-azetidin-1-yl-2-cyanocyclohexyl]-4-carbamoyl-1*H*-pyrazol-3-yl}amino)phenyl]-2-methylpropanoic acid;
2-[4-({1-[4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-4-carbamoyl-1*H*-pyrazol-3-yl}amino)phenyl]-2-methylpropanoic acid;
1-[2-cyano-4-(oxetan-3-ylamino)cyclohexyl]-3-{[4-(2,2,2-trifluoroethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(4-acetylphenyl)amino]-1-[4-azetidin-1-yl-2-cyanocyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(dimethylamino)cyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(3-methylazetidin-1-yl)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[4-(benzylamino)-2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{[(1S)-1-cyclopropylethyl]amino}cyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3-methoxyazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(4-chlorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[4-(difluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3-fluoroazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2,2,2-trifluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[4-(difluoromethoxy)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(4-chlorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2,2,2-trifluoroethyl)amino]cyclohexyl}-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3-fluoroazetidin-1-yl)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2,2-difluoroethyl)(methyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-3-[(4-cyanophenyl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(dimethylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(2-oxa-6-azaspiro[3.3]hept-6-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3-methylazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-3-({4-[(difluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(dimethylamino)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(dimethylamino)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(dimethylamino)cyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-[4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(cyclopropylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(cyclopropylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3-methylazetidin-1-yl)cyclohexyl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-[4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide,

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(3,3-dimethylazetidin-1-yl)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[4-(2-azaspiro[3.3]hept-2-yl)-2-cyanocyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(6-oxa-1-azaspiro[3.3]hept-1-yl)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3-methoxyazetidin-1-yl)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[2-(methylsulfonyl)ethyl]amino}cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2-methoxyethyl)(methyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3-hydroxyazetidin-1-yl)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[(1,1-dioxidotetrahydrothiophen-3-yl)methyl]amino}cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(1,1-dioxidotetrahydrothiophen-3-yl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[2-(dimethylsulfamoyl)ethyl]amino}cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(oxetan-3-ylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2R)-2-(fluoromethyl)pyrrolidin-1-yl]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(3S)-3-fluoropyrrolidin-1-yl]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

N-{4-[4-carbamoyl-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazol-1-yl]-3-cyanocyclohexyl}glycine;

1-{2-cyano-4-[(dicyclopropylmethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2,2-difluoroethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(3,3,3-trifluoropropyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[4-azetidin-1-yl-2-cyanocyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[methyl(3,3,3-trifluoropropyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(cyclopropylmethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(1-methylethyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[1-cyclopropylethyl]amino}cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(dicyclopropylmethyl)(methyl)amino]cyclohexyl}-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(dicyclopropylamino)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[(1R)-1-cyclopropylethyl]amino}cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(3-methylazetidin-1-yl)cyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(dimethylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[1-cyclopropylethyl]amino}cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-{[1-cyclopropyl-2,2,2-trifluoroethyl]amino}cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(2,2-dimethylazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[(2-cyano-4-(3-hydroxy-3-methylazetidin-1-yl)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[3-hydroxy-3-(trifluoromethyl)azetidin-1-yl]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[4-(tert-butylamino)-2-cyanocyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(1-methylcyclopropyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(3-methyloxetan-3-yl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(1-cyclopropyl-1-methylethyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(2-hydroxy-1,1-dimethylethyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{(2-cyano-4-[3-(1-hydroxy-1-methylethyl)azetidin-1-yl]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[3-hydroxy-3-(trifluoromethyl)azetidin-1-yl]cyclohexyl}-1H-pyrazole-4-carboxamide;

1-{2-cyano-4-[(1-cyclopropyl-1-methylethyl)amino]cyclohexyl}-3-(phenylamino)-1H-pyrazole-4-carboxamide;

1-[4-(tert-butylamino)-2-cyanocyclohexyl]-3-(phenylamino)-1H-pyrazole-4-carboxamide;

1-{2-cyano-4-[(1-methylcyclopropyl)amino]cyclohexyl}-3-(phenylamino)-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[(2-cyano-4-{[(3-methyloxetan-3-yl)methyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(tetrahydro-2H-pyran-4-ylamino)cyclohexyl]-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{methyl[(3-methyloxetan-3-yl)methyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{[(1-hydroxycyclopropyl)methyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(2-hydroxy-2-methylpropyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{[1-(hydroxymethyl)cyclopropyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-2-cyano-4-[(2,2,2-trifluoroethyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[(2-cyano-4-{[1-(trifluoromethyl)cyclopropyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(2-methoxy-2-methylpropyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(1-cyclopropyl-1-methylethyl)(methyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

1-{2-cyano-4-[(3-methyloxetan-3-yl)amino]cyclohexyl}-3-(phenylamino)-1H-pyrazole-4-carboxamide;

1-{(2-cyano-4-[(2-methoxy-1,1-dimethylethyl)amino]cyclohexyl}-3-(phenylamino)-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{(2-cyano-4-[methyl(3-methyloxetan-3-yl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

1-{2-cyano-4-[methyl(2,2,2-trifluoroethyl)amino]cyclohexyl}-3-[(2-fluoropyridin-4-yl)amino]-1H-pyrazole-4-carboxamide;

1-{2-cyano-4-[methyl(2,2,2-trifluoroethyl)amino]cyclohexyl}-3-[(2-fluoropyridin-4-yl)amino]-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(2-methoxy-1,1-dimethylethyl)(methyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(4-methyltetrahydro-2H-pyran-4-yl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(2-methoxyethyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[(2-cyano-4-{[(1S)-2-methoxy-1-methylethyl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(2-methoxyethyl)(methyl)amino]cyclohexyl}-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{[2-methoxy-1-methylethyl](methyl)amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{[(1S or 1R)-2-methoxy-1-methylethyl](methyl)amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

4-{4-Carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexanaminium trifluoroacetate;

1-{2-Cyano-4-[methyl(oxetan-3-yl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(cyclopropylmethyl)(methyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-({[3-(1-hydroxy-1-methylethyl)cyclobutyl]methyl}amino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[(2-cyano-4-(spiro[3.4]oct-2-ylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[cyclobutyl(cyclopropylmethyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(2-methylpropyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[cyclobutyl(methyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(cyclopropylmethyl)(2-methylpropyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(cyclopropylmethyl)(oxetan-3-yl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{(2-cyano-4-[(2,6-difluorobenzyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[(2-cyano-4-(cyclobutylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{4-[bis(cyclopropylmethyl)amino]-2-cyanocyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-{2-cyano-4-[(cyclobutylmethyl)amino]cyclohexyl}-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-(oxetan-3-ylamino)cyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-(4-(4-carbamoyl-3-((4-(trifluoromethyl)phenyl)amino)-1*H*-pyrazol-1-yl)-3-cyanocyclohexyl)-1-methylazetidin-1-ium 2,2,2-trifluoroacetate;

1-[4-{4-carbamoyl-3-[(4-chlorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl]-1-methylazetidinium;

1-[4-{4-carbamoyl-3-[(4-chlorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl]-1-ethylazetidinium;

1-[4-{4-carbamoyl-3-[(4-chlorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl]-1,3,3-trimethylazetidinium;

1-[4-{4-carbamoyl-3-[(4-chlorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl]-1-(cyclopropylmethyl)azetidinium;

3-[(4-Chloro-3-fluorophenyl)amino]-1-[2-cyano-4-cyclopropyl-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxy-4-methylcyclohexyl]-3-{[4-(3,3,3-trifluoro-hydroxy-1,1-dimethylpropyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxy-4-methylcyclohexyl]-3-{[4-(3,3,3-trifluoro-hydroxy-1,1-dimethylpropyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-ethenyl-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chloro-3-fluorophenyl)amino]-1-[2-cyano-4-hydroxy-4-methylcyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxy-4-methylcyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-hydroxy-4-methylcyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-cyclopropyl-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-(2-Cyano-4-hydroxycyclohexyl)-3-((4-(trifluoromethoxy)phenyl)amino)-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chloro-3-fluorophenyl)amino]-1-[2-cyano-4-hydroxycyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(trifluoromethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-[(4-cyanophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[6-(difluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[6-(trifluoromethyl)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxyethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-({4-[2,2,2-trifluoro-1-hydroxy-1-methylethyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[(2-cyano-4-hydroxycyclohexyl]-3-{[4-(3,3,3-trifluoro-hydroxy-1,1-dimethylpropyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-[(4-cyclopropylphenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(3-methyloxetan-3-yl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-[(3,4-dichlorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[4-(2-fluoro-1,1-dimethylethyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-{[6-(difluoromethoxy)pyridin-3-yl]amino}-1*H*-pyrazole-4-carboxamide;

4-{4-Carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl phenylcarbamate;

4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl cyclohexylcarbamate;

4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl phenylcarbamate;

4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl propan-2-ylcarbamate;

4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl methylcarbamate;

4-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-3-cyanocyclohexyl ethylcarbamate;

3-((4-chlorophenyl)amino)-1-(2-cyano-4-(3,3-dimethylazetidine-1-carbonyl)cyclohexyl)-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{[3-(1-hydroxy-1-methylethyl)azetidin-1-yl]carbonyl}cyclohexyl]-1*H*-pyrazole-4-carboxamide;

1-[4-(2-azaspiro[3.3]hept-2-ylcarbonyl)-2-cyanocyclohexyl]-3-[(4-chlorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(dicyclopropylmethyl)carbamoyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(3,3-difluoroazetidin-1-yl)carbonyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(oxetan-3-ylcarbamoyl)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{[3-(methylsulfonyl)azetidin-1-yl]carbonyl}cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(2,2,2-trifluoroethyl)carbamoyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(cyclobutylcarbamoyl)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{[1-cyclopropyl-2,2,2-trifluoroethyl]carbamoyl}cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(3,3-difluorocyclobutyl)carbamoyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(cyclopropylcarbamoyl)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(3-hydroxy-3-methylazetidin-1-yl)carbonyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(3,3-difluoropyrrolidin-1-yl)carbonyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-{[(3-methyloxetan-3-yl)methyl]carbamoyl}cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(3-fluoroazetidin-1-yl)carbonyl]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

1-[4-(tert-butylcarbamoyl)-2-cyanocyclohexyl]-3-[(4-chlorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-[2-cyano-4-(2-oxa-6-azaspiro[3.3]hept-6-ylcarbonyl)cyclohexyl]-1*H*-pyrazole-4-carboxamide;

3-(4-Chlorophenylamino)-1-(2-cyano-4-(2-hydroxypropan-2-yl)cyclohexyl)-1*H*-pyrazole-4-carboxamide;

1-[2-Cyano-4-(fluoromethyl)cyclohexyl]-3-[(2-fluoropyridin-4-yl)amino]-1*H*-pyrazole-4-carboxamide;

1-{2-Cyano-4-[(methylsulfonyl)amino]cyclohexyl}-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[(methylsulfonyl)amino]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

3-[(4-chlorophenyl)amino]-1-{2-cyano-4-[methyl(methylsulfonyl)amino]cyclohexyl}-1*H*-pyrazole-4-carboxamide;

1-[2-Cyanocyclohexyl]-3-({4-[(methoxyimino)methyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-Cyanocyclohexyl]-3-{[4-(N-methoxyethanimidoyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

4-(4-Carbamoyl-3-((4-(trifluoromethyl)phenyl)amino)-1*H*-pyrazol-1-yl)-5-cyano-2-hydroxycyclohexyl acetate;

1-[2-Cyanocyclohexyl]-3-{[4-(methylsulfonyl)phenyl]amino}-1*H*-pyrazole-4-carboxamide;

1-[2-Cyanocyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-[(4-fluorophenyl)amino]-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(difluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyanocyclohexyl]-3-({4-[(2,2,2-trifluoroethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

1-[2-cyano-4-hydroxycyclohexyl]-3-({4-[(trifluoromethyl)sulfonyl]phenyl}amino)-1*H*-pyrazole-4-carboxamide;

tert-Butyl [3-{4-carbamoyl-3-[(4-fluorophenyl)amino]-1*H*-pyrazol-1-yl}-4-cyanocyclohexyl]carbamate;

1-[8-Cyano-1,4-dioxaspiro[4.5]dec-7-yl]-3-(phenylamino)-1*H*-pyrazole-4-carboxamide; and

1-[2-cyanocyclohexyl]-3-[(1,1-dioxido-2,3-dihydro-1-benzothiophen-5-yl)amino]-1*H*-pyrazole-4-carboxamide.

3. A pharmaceutical composition comprising a compound of Claim 1 or a pharamceutically acceptable salt or a stereoisomer thereof and a pharmaceutically acceptable carrier.

4. 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 salt or stereoisomer thereof.

5. A method of treating a condition in a mammal that can be ameliorated by the selective inhibition of a Janus kinase JAK1 relative to 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.

6. A method according to Claim 5, wherein said condition is arthritis.

7. A method according to Claim 6, wherein said condition is selected from rheumatoid arthritis, juvenile arthritis, and psoriatic arthritis.

8. A method according to Claim 5, wherein said condition is asthma or obstructive airways diseases.

9. A method according to Claim 8, 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.

10. A method according to Claim 5, wherein said condition is autoimmune diseases or disorders.

11. 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 or stereoisomer thereof.

12. 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 or a stereoisomer thereof.

13. 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 desease or a disorder ameliorated by the selective inhibition of a Janus kinase JAK1 relative to JAK 2.

14. 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 desease or a disorder ameliorated by the selective inhibition of a Janus kinase JAK1 relative to JAK 2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/001291

A. CLASSIFICATION OF SUBJECT MATTER

See 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: C07D231/-, A61K31/-, A61P37/-, A61P35/-

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)

WPI, EPODOC, CNPAT, CNKI, CA: cycloalkylnitrile, pyrazole, carboxamide?, Janus, JAK, kinase, inhibit+

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO2010/014453A1(MERCK & CO., INC. et al.) 04 Feb. 2010 (04.02.2010) the whole document	1-14
A	WO2010/099379A1(AMBIT BIOSCIENCES CORPORATION et al.) 02 Sep. 2010 (02.09.2010) the whole document	1-14

☐ 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
10 Dec. 2012(10.12.2012)	**27 Dec. 2012 (27.12.2012)**
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 LIU, Guangyu Telephone No. (86-10)82246723

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/001291

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.: 4-12
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 4-12 are directed to the methods for the treatment of human or animal body by therapy. But the search has been carried out and based on the following subject matter: the use of a compound according to any one of claims in the manufacture of medicaments for the treatment of diseases.

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/CN2012/001291

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO2010/014453A1	04.02.2010	AU2009276873A1	04.02.2010
		CA2732038A1	04.02.2010
		EP2341775A4	28.09.2011
		EP2341775A1	13.07.2011
		JP2011529891A	15.12.2011
		US2011/0130393A1	02.06.2011
WO2010/099379A1	02.09.2010	AU2010217929A1	08.09.2011
		CA2752885A1	02.09.2010
		CN102395576A	28.03.2012
		EP2401267A1	04.01.2012
		IL214768D0	30.11.2011
		JP2012519179A	23.08.2012
		MX2011008995A	15.09.2011
		SG173852A1	29.09.2011
		US2010/0317659A1	16.12.2010
		AR075633A1	20.04.2011
		KR20110124787A	17.11.2011
		TW201041875A	01.12.2010
		WO2010/099379A8	25.11.2010

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/001291

Continuation of: "A. CLASSIFICATION OF SUBJECT MATTER":

C07D231/10(2006.01)i

A61K31/415(2006.01)i

A61P37/00(2006.01)i

A61P35/00(2006.01)i