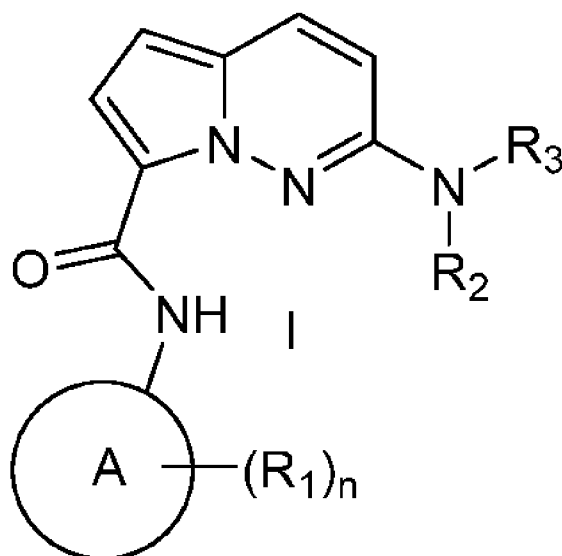




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[Continued on next page]

(54) **Title:** PYRROLOPYRIDAZINE INHIBITORS OF IRAK4 ACTIVITY

(57) **Abstract:** The present invention relates to pyrrolopyridazine inhibitors of IRAK4 of formula (I) and provides compositions comprising such inhibitors, as well as methods therewith for treating IRAK4-mediated or -associated conditions or diseases.

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- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
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TITLE OF THE INVENTION

PYRROLOPYRIDAZINE INHIBITORS OF IRAK4 ACTIVITY

BACKGROUND OF THE INVENTION

5 The present invention is directed to compounds which modulate interleukin-1 (IL-1) receptor-associated kinase 4 (IRAK4) and are useful in the prevention or treatment of inflammatory, cell proliferative and immune-related conditions and diseases.

 The recruitment of immune cells to sites of injury involves the concerted interactions of a large number of soluble mediators. Several cytokines appear to play key roles in these processes, particularly IL-1 and TNF. Both cytokines are derived from mononuclear cells and macrophages, along with other cell types. Physiologically, they produce many of the same proinflammatory responses, including fever, sleep and anorexia, mobilization and activation of polymorphonuclear leukocytes, induction of cyclooxygenase and lipoxygenase enzymes, increase in adhesion molecule expression, activation of B-cells, T-cells and natural killer cells, and stimulation of production of other cytokines. Other actions include a contribution to the tissue degeneration observed in chronic inflammatory conditions, such as stimulation of fibroblast proliferation, induction of collagenase, etc. They have also been implicated in the process of bone resorption and adipose tissue regulation. Thus, these cytokines play key roles in a large number of pathological conditions, including rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, diabetes, obesity, cancer, sepsis, etc.

 The importance of IL-1 in inflammation has been demonstrated by the ability of the highly specific IL-1 receptor antagonist protein (IL-1Ra or IRAP) to relieve inflammatory conditions. See, e.g., Dinarello, Cytokine Growth Factor Rev., 1997, 8:253-265.

 IL-1 treatment of cells induces the formation of a complex consisting of the two IL-1 receptor chains, IL-1R1 and IL-1RAcP, and the resulting heterodimer recruits an adaptor molecule designated as MyD88. See e.g., Wesche et al., J. Biol. Chem., 1999, 274:19403-19410. MyD88 binds to a protein designated IRAK (IL-1 receptor associated kinase). See, e.g., O'Neill et al., J. Leukoc. Biol., 1998, 63(6):650-657; Auron, Cytokine Growth Factor Rev., 1998, 9(3-4):221-237; and O'Neill, Biochem. Soc. Trans., 2000, 28(5):557-563. IRAK is subsequently phosphorylated and released from the receptor complex to interact with a tumor necrosis factor receptor-associated factor, TRAF6, which transduces the signal to downstream effector molecules. See e.g., Cao et al., Nature, 1996, 383:443-446. TRAF6 can trigger the NIK/IKK kinase cascade to activate the transcription factor NF-kappa B. NF-kappa B regulates a number of genes that, in turn, regulate immune and inflammatory responses.

 Four IRAKs have been identified: IRAK1 (see, e.g., Cao et al., Science, 1996, 271:1128-1131), IRAK2 (see, e.g. Muzio et al., Science, 1997, 278:1612-1615), the monomyeloic cell specific IRAKM, also known as IRAK3 (see, e.g., Wesche et al., J. Biol.

Chem., 1999, 274:19403-19410), and IRAK4 (see, e.g., PCT Publication No. WO 01/051641). IRAK proteins have been shown to play a role in transducing signals other than those originating from IL-1 receptors, including signals triggered by activation of IL-18 receptors (see, e.g., Kanakaraj et al., J. Exp. Med., 1999, 189(7):1129-1138) and LPS receptors (see, e.g., Yang et al., J. Immunol., 1999, 163:639-643; and Wesche et al., J. Biol. Chem., 1999, 274:19403-19410). Over-expression of IRAK2 and IRAKM has been shown to be capable of reconstituting the response to IL-1 and LPS in an IRAK deficient cell line.

The identification of compounds that inhibit the function of IRAK4 represents an attractive approach to the development of therapeutic agents for the treatment of inflammatory, cell proliferative and immune-related conditions and diseases associated with IRAK4-mediated signal transduction, such as rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, diabetes, obesity, allergic disease, psoriasis, asthma, graft rejection, cancer, and sepsis.

It is an object of the instant invention to provide novel compounds that are inhibitors of IRAK4.

It is also an object of the present invention to provide pharmaceutical compositions that comprise the novel compounds that are inhibitors of IRAK4.

It is also an object of the present invention to provide a method for treating IRAK4-mediated and associated conditions or diseases that comprises administering such inhibitors of IRAK4 activity.

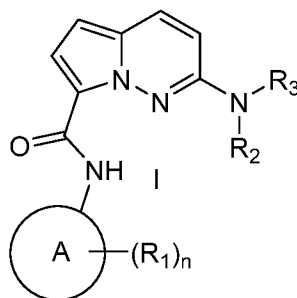
SUMMARY OF THE INVENTION

The present invention relates to pyrrolopyridazine inhibitors of IRAK4 of formula (I) and provides compositions comprising such inhibitors, as well as methods therewith for treating IRAK4-mediated or -associated conditions or diseases.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the instant invention are useful in the inhibition of the activity of IRAK4.

An embodiment of the instant invention is illustrated by the Formula I:



wherein:

Ring A is aryl or heterocyclyl;

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

R₁ is independently selected from: (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, heterocyclyl,
 5 CF₃, CHF₂, CN, halo, said alkyl, cycloalkyl and heterocyclyl optionally substituted with halo,
 OH, CH₃, and OCH₃;

R₂ is H and R₃ is independently selected from: (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl
 and heterocyclyl each optionally substituted with one or more halo, OH, N(R_b)₂, or morpholinyl,
 or R₂ and R₃ can be taken together with the nitrogen to which they are attached to form
 10 heterocyclyl, said heterocyclyl optionally substituted with one or more substituents selected from
 R_a;

R_a is independently selected from (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, CF₃, CHF₂,
 OH, halo and NH₂, said alkyl optionally substituted with (C₃-C₆)cycloalkyl and CF₃; and

R_b is independently selected from H and (C₁-C₄)alkyl;
 15 or a pharmaceutically acceptable salt thereof.

Another embodiment of the instant invention is illustrated by the Formula I:

wherein:

Ring A is pyrazolyl, pyridinyl, thiophenyl, furanyl or phenyl;

n is 0, 1 or 2;

R₁ is independently selected from: (C₁-C₄)alkyl, cyclopropyl, oxadiazolyl,
 20 pyridinyl, oxazolyl, triazolyl, pyrimidinyl, CF₃, CHF₂, CN and halo, said alkyl, oxadiazolyl,
 pyridinyl, oxazolyl, triazolyl and pyrimidinyl are optionally substituted with halo, OH, CH₃, and
 OCH₃;

R₂ is H and R₃ is independently selected from: (C₁-C₄)alkyl, cyclohexyl,
 25 cycloheptyl, piperidinyl and azepanyl each optionally substituted with one or more F, OH,
 N(R_b)₂, or morpholinyl, or R₂ and R₃ can be taken together with the nitrogen to which they are
 attached to form a heterocyclyl selected from piperazinyl, diazepanyl, diazabicyclooctyl,
 diazabicycloheptyl, diazaspirononyl, hexahydropyrrolopyrazinyl, piperidinyl, diazabicyclononyl,
 oxadiazabicyclodecyl and diazatricyclodecyl, said heterocyclyl optionally substituted with one or
 30 more substituents selected from R_a;

R_a is independently selected from (C₁-C₄)alkyl, cyclopropyl, CF₃, CHF₂, OH, F
 and NH₂, said alkyl optionally substituted with cyclopropyl and CF₃; and

R_b is independently selected from H and methyl;
 or a pharmaceutically acceptable salt thereof.

35 A compound selected from:

2-[(1R,2S)-2-aminocyclohexyl]amino}-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-
 yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

- 2-(3,6-diazabicyclo[3.2.1]oct-3-yl)-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-[(1S,5S)-3,6-diazabicyclo[3.2.1]oct-3-yl]-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
5 2-[(1R,5R)-3,6-diazabicyclo[3.2.1]oct-3-yl]-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-[(1R,2S)-2-hydroxycyclohexyl]amino}-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]-2-[(3R)-piperidin-3-ylamino]pyrrolo[1,2-
10 b]pyridazine-7-carboxamide;
2-[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-(2,5-diazabicyclo[2.2.2]oct-2-yl)-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
15 2-(5,8-diazaspiro[2.6]non-5-yl)-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-(1,4-diazepan-1-yl)-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-(2,5-diazabicyclo[2.2.2]oct-2-yl)-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
20 2-[(3R)-3-aminopiperidin-1-yl]-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-[(3R)-3-aminopiperidin-1-yl]-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
25 N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]-2-piperazin-1-ylpyrrolo[1,2-b]pyridazine-7-carboxamide;
2-(1,4-diazepan-1-yl)-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]-2-[(3R)-piperidin-3-ylamino]pyrrolo[1,2-
30 b]pyridazine-7-carboxamide;
2-(2,5-diazabicyclo[2.2.2]oct-2-yl)-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-(5,8-diazaspiro[2.6]non-5-yl)-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
35 2-[(1R,2S)-2-aminocyclohexyl]amino}-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

- N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]-2-{{(1R,2S)-2-hydroxycyclohexyl}amino}pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(3-bromo-1-methyl-1H-pyrazol-4-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
5 2-{{(1R,2S)-2-aminocyclohexyl}amino}-N-(3-bromo-1-methyl-1H-pyrazol-4-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(3-chloro-1-methyl-1H-pyrazol-4-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-(azepan-3-ylamino)-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
10 2-{{(1R,2S)-2-aminocyclohexyl}amino}-N-(3-chloro-1-methyl-1H-pyrazol-4-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(3-chloro-1-methyl-1H-pyrazol-4-yl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
15 N-(3-bromo-1-methyl-1H-pyrazol-4-yl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-{{(1R,2R)-2-amino-3,3-difluorocyclohexyl}amino}-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-{{(1R,2S)-2-aminocyclohexyl}amino}-N-(3-cyano-1-methyl-1H-pyrazol-4-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
20 N-(3-cyano-1-methyl-1H-pyrazol-4-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(3-cyano-1-methyl-1H-pyrazol-4-yl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
25 2-{{(1R,2R)-2-amino-3,3-difluorocyclohexyl}amino}-N-(3-bromo-1-methyl-1H-pyrazol-4-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(3-chloro-1-methyl-1H-pyrazol-4-yl)-2-[(1S,4S)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(3-chloro-1-methyl-1H-pyrazol-4-yl)-2-[(1R,4R)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
30 N-(3-bromo-1-methyl-1H-pyrazol-4-yl)-2-[(1S,4S)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(3-bromo-1-methyl-1H-pyrazol-4-yl)-2-[(1R,4R)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
35 2-[(1S,4S)-2,5-diazabicyclo[2.2.2]oct-2-yl]-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

- 2-[(1R,4R)-2,5-diazabicyclo[2.2.2]oct-2-yl]-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-[(3R)-azepan-3-ylamino]-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 5 2-[(3S)-azepan-3-ylamino]-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-[(3R)-azepan-3-ylamino]-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-[(3S)-azepan-3-ylamino]-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 10 N-(3-cyano-1-methyl-1H-pyrazol-4-yl)-2-[(1S,4S)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- N-(3-cyano-1-methyl-1H-pyrazol-4-yl)-2-[(1R,4R)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 15 2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-[1-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-(3,8-diazabicyclo[3.2.1]oct-3-yl)-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-(3,8-diazabicyclo[3.2.1]oct-3-yl)-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 20 2-{[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(3-chloro-1-methyl-1H-pyrazol-4-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-(3,6-diazabicyclo[3.2.1]oct-3-yl)-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 25 2-[(1S,5S)-3,6-diazabicyclo[3.2.1]oct-3-yl]-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-[(1R,5R)-3,6-diazabicyclo[3.2.1]oct-3-yl]-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-{[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(3-cyano-1-methyl-1H-pyrazol-4-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 30 N-(3-chloro-1-methyl-1H-pyrazol-4-yl)-2-{[(1R,2S)-2-hydroxycyclohexyl]amino}pyrrolo[1,2-b]pyridazine-7-carboxamide;
- N-[1-tert-butyl-3-(difluoromethyl)-1H-pyrazol-4-yl]-2-{[(1R,2S)-2-hydroxycyclohexyl]amino}pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 35 N-[3-(difluoromethyl)-1-(1-methylethyl)-1H-pyrazol-4-yl]-2-{[(1R,2S)-2-hydroxycyclohexyl]amino}pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-(2,5-diazabicyclo[2.2.2]oct-2-yl)-N-[4-(difluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-bromophenyl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-(2-bromophenyl)pyrrolo[1,2-b]pyridazine-7-
5 carboxamide;
N-(2-chlorophenyl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(4-bromothiophen-3-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-bromophenyl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(4-bromothiophen-3-yl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-
10 carboxamide;
2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-(4-bromothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-
carboxamide;
N-(2-chlorophenyl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-(2-chlorophenyl)pyrrolo[1,2-b]pyridazine-7-
15 carboxamide;
N-(2-chlorothiophen-3-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-cyanothiophen-3-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(4-cyanothiophen-3-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-(1,4-diazepan-1-yl)-N-[4-(difluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-
20 carboxamide;
N-(2-chlorothiophen-3-yl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-
carboxamide;
2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-(2-chlorothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-
carboxamide;
25 2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-[4-(difluoromethyl)thiophen-3-yl]pyrrolo[1,2-
b]pyridazine-7-carboxamide;
2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-(4-cyanothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-
carboxamide;
N-(4-cyanothiophen-3-yl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-
30 carboxamide;
2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-(2-cyanothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-
carboxamide;
N-(2-bromothiophen-3-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-(2-bromothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-
35 carboxamide;
N-(2-bromothiophen-3-yl)-2-[(1S,4S)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-
7-carboxamide;

- N-(2-bromothiophen-3-yl)-2-[(1R,4R)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- N-(2-cyanothiophen-3-yl)-2-[(1S,4S)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 5 N-(2-cyanothiophen-3-yl)-2-[(1R,4R)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- N-(4-chlorothiophen-3-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- N-(4-chlorothiophen-3-yl)-2-[(1S,4S)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 10 N-(4-chlorothiophen-3-yl)-2-[(1R,4R)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-[(1R,2S)-2-aminocyclohexyl]amino}-N-(4-chlorothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(2-bromothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 15 2-[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(4-chlorothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(4-bromothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 20 2-[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(4-cyanothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(2-chlorothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- N-(2-chlorothiophen-3-yl)-2-[(1R,2S)-2-hydroxycyclohexyl]amino}pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 25 2-[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(2-chlorophenyl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- N-(2-chlorophenyl)-2-[(1R,2S)-2-hydroxycyclohexyl]amino}pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 30 2-[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(2-bromophenyl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- N-(2-bromophenyl)-2-[(1R,2S)-2-hydroxycyclohexyl]amino}pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-[4-(difluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 35 N-(2-cyanothiophen-3-yl)-2-[(1R,2S)-2-hydroxycyclohexyl]amino}pyrrolo[1,2-b]pyridazine-7-carboxamide;

- 2-{[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(2-cyanothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]-2-piperazin-1-ylpyrrolo[1,2-b]pyridazine-7-carboxamide;
- 5 N-(2-cyanophenyl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-cyanophenyl)-2-piperazin-1-ylpyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-cyanophenyl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-cyanophenyl)-2-(5,8-diazaspiro[2.6]non-5-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-cyanophenyl)-2-{[(1R,2S)-2-hydroxycyclohexyl]amino}pyrrolo[1,2-b]pyridazine-7-
- 10 carboxamide;
N-(2-cyanophenyl)-2-[(3R)-piperidin-3-ylamino]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-(2-cyanophenyl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-[(3R)-3-aminopiperidin-1-yl]-N-(2-cyanophenyl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 15 2-[(3R)-azepan-3-ylamino]-N-(2-cyanophenyl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-[(3S)-azepan-3-ylamino]-N-(2-cyanophenyl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-{[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(2-cyanophenyl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-[2-(trifluoromethyl)phenyl]pyrrolo[1,2-b]pyridazine-
- 20 7-carboxamide;
2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-[2-(difluoromethyl)phenyl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-[(1S,4S)-2,5-diazabicyclo[2.2.2]oct-2-yl]-N-[2-(trifluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 25 2-[(1R,4R)-2,5-diazabicyclo[2.2.2]oct-2-yl]-N-[2-(trifluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-(1,4-diazepan-1-yl)-N-[2-(trifluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-[2-(trifluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 30 2-{[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-[2-(trifluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-{[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-[2-(difluoromethyl)phenyl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 35 2-(3,8-diazabicyclo[3.2.1]oct-8-yl)-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

- 2-(3,8-diazabicyclo[3.2.1]oct-8-yl)-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-(3,6-diazabicyclo[3.2.1]oct-6-yl)-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
5 2-[(1S,5R)-3,6-diazabicyclo[3.2.1]oct-6-yl]-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-[(1R,5S)-3,6-diazabicyclo[3.2.1]oct-6-yl]-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-(3,6-diazabicyclo[3.2.1]oct-6-yl)-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
10 2-[(1S,5R)-3,6-diazabicyclo[3.2.1]oct-6-yl]-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide; and
2-[(1R,5S)-3,6-diazabicyclo[3.2.1]oct-6-yl]-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
15 or a pharmaceutically acceptable salt thereof.

When any variable (e.g. R_a, etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents represent that the indicated bond may be
20 attached to any of the substitutable ring atoms. If the ring system is bicyclic, it is intended that the bond be attached to any of the suitable atoms on either ring of the bicyclic moiety.

It is understood that one or more silicon (Si) atoms can be incorporated into the compounds of the instant invention in place of one or more carbon atoms by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by
25 techniques known in the art from readily available starting materials. Carbon and silicon differ in their covalent radius leading to differences in bond distance and the steric arrangement when comparing analogous C-element and Si-element bonds. These differences lead to subtle changes in the size and shape of silicon-containing compounds when compared to carbon. One of ordinary skill in the art would understand that size and shape differences can lead to subtle or
30 dramatic changes in potency, solubility, lack of off target activity, packaging properties, and so on. (Diass, J. O. et al. *Organometallics* (2006) 5:1188-1198; Showell, G.A. et al. *Bioorganic & Medicinal Chemistry Letters* (2006) 16:2555-2558).

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

the same carbon or on different carbons, so long as a stable structure results. In some instances, two substituents are attached to the same carbon and come together to form a carbocyclic or heterocyclic ring (a spirocyclic ring system).

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C₁-C₆, as in "(C₁-C₆)alkyl" is defined to include groups having 1, 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement. For example, "(C₁-C₆)alkyl" specifically includes methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *i*-butyl, pentyl, hexyl, and so on. For example, C₁-C₄, as in "(C₁-C₄)alkyl" is defined to include groups having 1, 2, 3 or 4 carbons in a linear or branched arrangement. For example, "(C₁-C₄)alkyl" specifically includes methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl and *i*-butyl.

The term "cycloalkyl" means a monocyclic saturated aliphatic hydrocarbon group having the specified number of carbon atoms. For example, "cycloalkyl" includes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, and so on.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydro-naphthyl, indanyl and biphenyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 3- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, and includes spiro, bicyclic and tricyclic groups. "Heterocyclyl" therefore includes heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: benzoimidazolyl, benzoimidazolonyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolaziny, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazoliny, quinolyl, quinoxaliny, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidiny, 1,4-dioxanyl, hexahydroazepiny, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinoliny, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidiny, methylenedioxybenzoyl,

tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro (Cl), fluoro (F), bromo (Br) and iodo (I).

5 The compounds of this invention include the salts, solvates, hydrates or prodrugs of the compounds. The use of the terms "salt", "solvate", "hydrate", "prodrug" and the like, is intended to equally apply to the salt, solvate, hydrate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, or racemates of the inventive compounds.

SALTS

10 The IRAK4 inhibitor compounds of the present invention, which can be in the form of a free base, may be isolated from the reaction mixture in the form of a pharmaceutically acceptable salt.

The compounds of Formula I can form salts which are also within the scope of this invention. Reference to a compound of Formula I herein is understood to include reference
15 to pharmaceutically acceptable salts thereof, unless otherwise indicated. The term "pharmaceutically acceptable salt(s)" or "salt", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula I contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic
20 acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Such acidic and basic salts used within the scope of the invention are pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts. Salts of the compounds of Formula I may be formed, for example, by reacting a compound of Formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in
25 an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates,
30 sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl et al, Camille G. (eds.) Handbook of Pharmaceutical Salts. Properties, Selection and Use. (2002) Zurich: Wiley-VCH; S. Berge et al, Journal of Pharmaceutical Sciences (1977)
35 66(1) 1-19; P. Gould, International J. of Pharmaceutics (1986) 33 201-217; Anderson et al, The Practice of Medicinal Chemistry (1996), Academic Press, New York; and in The Orange Book

(Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g., methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g., decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g., benzyl and phenethyl bromides), and others.

CRYSTALS

The IRAK4 inhibitor compounds of the present invention may exist as amorphous forms or crystalline forms.

The compounds of Formula I may have the ability to crystallize in more than one form, a characteristic known as polymorphism, and it is understood that such polymorphic forms ("polymorphs") are within the scope of Formula I. Polymorphism generally can occur as a response to changes in temperature or pressure or both and can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility and melting point.

SOLVATES

The compounds having Formula I or the pharmaceutically acceptable salts may form hydrates or solvates. It is known to those of skill in the art that charged compounds form hydrated species when lyophilized with water, or form solvated species when concentrated in a solution with an appropriate organic solvent. The compounds of this invention include the hydrates or solvates of the compounds listed.

One or more compounds of the invention having Formula I or the pharmaceutically acceptable salts or solvates thereof may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanlates, methanlates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H₂O.

Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.* 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example IR spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

OPTICAL ISOMERS

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. Such stereoisomeric forms also include enantiomers and diastereoisomers, *etc*.

For chiral compounds, methods for asymmetric synthesis whereby the pure stereoisomers are obtained are well known in the art, *e.g.* synthesis with chiral induction, synthesis starting from chiral intermediates, enantioselective enzymatic conversions, separation of stereoisomers using chromatography on chiral media. Such methods are described in *Chirality in Industry* (edited by A.N. Collins, G.N. Sheldrake and J. Crosby, 1992; John Wiley). Likewise methods for synthesis of geometrical isomers are also well known in the art.

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
5 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. 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
10 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.

PRODRUGS

A discussion of prodrugs is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems (1987) 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term "prodrug" means a compound (e.g. a drug precursor) that is transformed in vivo to yield a compound of Formula I or a pharmaceutically acceptable salt,
20 hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g. by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press,
25 1987.

ISOTOPES

In the compounds of 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
30 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 (^1H) and deuterium (^2H). 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
35 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.

Certain isotopically-labelled compounds of Formula I (e.g. those labeled with ^3H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^3H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled compounds of Formula I can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by substituting an appropriate isotopically labeled reagent for a non-isotopically labeled reagent.

UTILITY

According to another embodiment, the present invention provides a method of treating or reducing the severity of a disease in a patient by using a compound of Formulas I as described above, wherein said disease is selected from IRAK4 mediated pathologies, such as rheumatoid arthritis, multiple sclerosis, sepsis, osteoarthritis, inflammatory bowel disease, Parkinson's disease, cardiac contractile dysfunction, type I diabetes, type II diabetes or familial cold autoinflammatory syndrome, allergic disease, cancer, lupus, psoriasis, asthma or graft rejection.

The compounds of the invention find use in a variety of applications. As will be appreciated by those skilled in the art, the kinase activity of IRAK4 may be modulated in a variety of ways; that is, one can affect the phosphorylation/activation of IRAK4 either by modulating the initial phosphorylation of the protein or by modulating the autophosphorylation of the other active sites of the protein. Alternatively, the kinase activity of IRAK4 may be modulated by affecting the binding of a substrate of IRAK4 phosphorylation.

The compounds of the invention are used to treat or prevent inflammation related diseases. Disease states which can be treated by the methods and compositions provided herein include, but are not limited to, cancer, autoimmune disease, viral disease, fungal disease, neurological/neurodegenerative disorders, arthritis, inflammation, anti-proliferative (e.g. ocular retinopathy), neuronal, alopecia, cardiovascular disease, graft rejection, inflammatory bowel disease, proliferation induced after medical procedures, including, but not limited to, surgery, angioplasty, and the like. It is appreciated that in some cases the cells may not be in a hyper- or hypoproliferation state (abnormal state) and still require treatment. Thus, in one embodiment, the invention herein includes application to cells or individuals which are afflicted or may eventually become afflicted with any one of these disorders or states.

The compounds of this invention may be administered to mammals, including humans, either alone or, in combination with pharmaceutically acceptable carriers, excipients or

diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous and topical routes of administration.

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, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone 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 mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropylmethyl-cellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate butyrate may be employed.

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 ingredient is mixed with water soluble carrier such as polyethyleneglycol 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, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, 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.

5 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
10 preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

 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
15 excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

 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
20 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, flavouring agents, preservatives and antioxidants.

25 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, flavoring and coloring agents and antioxidant.

 The pharmaceutical compositions may be in the form of sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's
30 solution and isotonic sodium chloride solution.

 The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulsion.

35 The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of

the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

5 The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. 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. In addition, sterile,
10 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.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical
15 application shall include mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will,
20 of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

When a composition according to this invention is administered into a human
25 subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

The dosage regimen utilizing the compounds of the instant invention can be selected in accordance with a variety of factors including type, age, weight, sex; the route of
30 administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to treat, for example, to prevent, inhibit (fully or partially) or arrest the progress of the disease. For example, compounds of the instant invention can be administered in a total daily dose of up to 10,000 mg. Compounds of the instant
35 invention can be administered once daily (QD), or divided into multiple daily doses such as twice daily (BID), and three times daily (TID). Compounds of the instant invention can be administered at a total daily dosage of up to 10,000 mg, e.g., 2,000 mg, 3,000 mg, 4,000 mg,

6,000 mg, 8,000 mg or 10,000 mg, which can be administered in one daily dose or can be divided into multiple daily doses as described above.

For example, compounds of the instant invention can be administered in a total daily dose of up to 1,000 mg. Compounds of the instant invention can be administered once daily (QD), or divided into multiple daily doses such as twice daily (BID), and three times daily (TID). Compounds of the instant invention can be administered at a total daily dosage of up to 1,000 mg, e.g., 200 mg, 300 mg, 400 mg, 600 mg, 800 mg or 1,000 mg, which can be administered in one daily dose or can be divided into multiple daily doses as described above.

In addition, the administration can be continuous, i.e., every day, or intermittently. The terms “intermittent” or “intermittently” as used herein means stopping and starting at either regular or irregular intervals. For example, intermittent administration of a compound of the instant invention may be administration one to six days per week or it may mean administration in cycles (e.g. daily administration for two to eight consecutive weeks, then a rest period with no administration for up to one week) or it may mean administration on alternate days.

In addition, the compounds of the instant invention may be administered according to any of the schedules described above, consecutively for a few weeks, followed by a rest period. For example, the compounds of the instant invention may be administered according to any one of the schedules described above from two to eight weeks, followed by a rest period of one week, or twice daily at a dose of 100 - 500 mg for three to five days a week. In another particular embodiment, the compounds of the instant invention may be administered three times daily for two consecutive weeks, followed by one week of rest.

Any one or more of the specific dosages and dosage schedules of the compounds of the instant invention, may also be applicable to any one or more of the therapeutic agents to be used in the combination treatment (hereinafter referred to as the “second therapeutic agent”).

Moreover, the specific dosage and dosage schedule of this second therapeutic agent can further vary, and the optimal dose, dosing schedule and route of administration will be determined based upon the specific second therapeutic agent that is being used.

Of course, the route of administration of the compounds of the instant invention is independent of the route of administration of the second therapeutic agent. In an embodiment, the administration for a compound of the instant invention is oral administration. In another embodiment, the administration for a compound of the instant invention is intravenous administration. Thus, in accordance with these embodiments, a compound of the instant invention is administered orally or intravenously, and the second therapeutic agent can be administered orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation,

vaginally, intraocularly, via local delivery by catheter or stent, subcutaneously, intraadiposally, intraarticularly, intrathecally, or in a slow release dosage form.

In addition, a compound of the instant invention and second therapeutic agent may be administered by the same mode of administration, i.e. both agents administered e.g. orally, by IV. However, it is also within the scope of the present invention to administer a compound of the instant invention by one mode of administration, e.g. oral, and to administer the second therapeutic agent by another mode of administration, e.g. IV or any other ones of the administration modes described hereinabove.

The first treatment procedure, administration of a compound of the instant invention, can take place prior to the second treatment procedure, i.e., the second therapeutic agent, after the treatment with the second therapeutic agent, at the same time as the treatment with the second therapeutic agent, or a combination thereof. For example, a total treatment period can be decided for a compound of the instant invention. The second therapeutic agent can be administered prior to onset of treatment with a compound of the instant invention or following treatment with a compound of the instant invention.

The instant compounds are also useful in combination with other therapeutic agents. Combinations of the presently disclosed compounds with therapeutic agents are within the scope of the invention. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the pathologies involved. The instant compounds are also useful in combination with known therapeutic agents.

The instant compounds are useful in combination with a known anti-inflammatory agent. In one embodiment, the anti-inflammatory agent is a nonsteroidal anti-inflammatory drug (NSAID). In one embodiment, the NSAID is selected from the group consisting of salicylates, indomethacin, flurbiprofen, diclofenac, ketorolac, naproxen, piroxicam, tebufelone, ibuprofen, etodolac, nabumetone, tenidap, alcofenac, antipyrine, aminopyrine, dipyrone, aminopyrnone, phenylbutazone, clofezone, oxyphenbutazone, prenazone, apazone, benzydamine, bucolome, cinchophen, clonixin, ditrazol, epirizole, fenoprofen, floctafenin, flufenamic acid, glaphenine, indoprofen, ketoprofen, loxoprofen, meclofenamic acid, mefenamic acid, niflumic acid, phenacetin, salidifamides, sulindac, suprofen, tolmetin, a pharmaceutically acceptable salt thereof, and a mixture thereof.

In another embodiment, the NSAID is a selective COX-2 inhibitor. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC₅₀ for COX-2 over IC₅₀ for COX-1 evaluated by cell or microsomal assays. Such compounds include, but are not limited to those disclosed in U.S. Pat. 5,474,995, U.S. Pat. 5,861,419, U.S. Pat. 6,001,843, U.S. Pat. 6,020,343, U.S. Pat. 5,409,944, U.S. Pat. 5,436,265,

U.S. Pat. 5,536,752, U.S. Pat. 5,550,142, U.S. Pat. 5,604,260, U.S. 5,698,584, U.S. Pat. 5,710,140, WO 94/15932, U.S. Pat. 5,344,991, U.S. Pat. 5,134,142, U.S. Pat. 5,380,738, U.S. Pat. 5,393,790, U.S. Pat. 5,466,823, U.S. Pat. 5,633,272, and U.S. Pat. 5,932,598, all of which are hereby incorporated by reference.

5 Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to: parecoxib, CELEBREX® and BEXTRA® or a pharmaceutically acceptable salt thereof.

 Those skilled in the art will realize that the term “cancer” to be the name for diseases in which the body’s cells become abnormal and divide without control.

10 Cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma) colorectal; Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal

cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma), breast; Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

In one embodiment, cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: lung cancer, pancreatic cancer, colon cancer, colorectal cancer, myeloid leukemias, acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelomonocytic leukemia, thyroid cancer, myelodysplastic syndrome, bladder carcinoma, epidermal carcinoma, melanoma, breast cancer, prostate cancer, head and neck cancers, ovarian cancer, brain cancers, cancers of mesenchymal origin, sarcomas, tetracarzinomas, neuroblastomas, kidney carcinomas, hepatomas, non-Hodgkin's lymphoma, multiple myeloma, and anaplastic thyroid carcinoma.

In another embodiment, cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: breast, prostate, colon, colorectal, lung, brain, testicular, stomach, pancreas, skin, small intestine, large intestine, throat, head and neck, oral, bone, liver, bladder, kidney, thyroid and blood.

In another embodiment, cancers that may be treated by the compounds, compositions and methods of the invention include breast, prostate, colon, ovary, endometrium and thyroid.

In another embodiment, cancers that may be treated by the compositions and methods of the invention include acute myeloid leukemia (AML), liposarcoma, colorectal cancer, gastric cancer and melanoma.

In a further embodiment, cancers that may be treated by the compositions and methods of the invention include hematological malignancies, for example acute myeloid leukemia.

In a further embodiment, cancers that may be treated by the compositions and methods of the invention include acute lymphoblastic leukemia (ALL), lymphoma, lung, breast and glioblastoma.

The compounds of the invention are also useful in preparing a medicament that may be useful in treating cancer. In one embodiment, the compounds of the invention are for the potential treatment of cancer.

The compounds of the invention may be useful to the treatment of a variety of
5 cancers, including, but not limited to: carcinoma, including, but not limited to, of the bladder, breast, colon, rectum, endometrium, kidney, liver, lung, head and neck, esophagus, gall bladder, cervix, pancreas, prostate, larynx, ovaries, stomach, uterus, sarcoma and thyroid cancer; hematopoietic tumors of the lymphoid lineage, including leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell
10 lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, mantle cell lymphoma, myeloma, and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma,
15 neuroblastoma, glioma, and schwannomas; and other tumors, including melanoma, skin (non-melanomal) cancer, mesothelioma (cells), seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratocanthoma, thyroid follicular cancer and Kaposi's sarcoma.

The compounds of the invention may be useful for the treatment of activated B-cell-like diffuse large B-cell lymphoma (ABC-DLBCL), chronic lymphocytic leukemia (CLL)
20 and Waldenström's Macroglobulinemia.

The instant compounds are useful in combination with a known anti-cancer agent. Combinations of the presently disclosed compounds with anti-cancer agents are within the scope of the invention. Examples of such anti-cancer agents can be found in Cancer Principles and Practice of Oncology by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001),
25 Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such agents include the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase
30 inhibitors and other angiogenesis inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, inhibitors of cell proliferation and survival signaling, bisphosphonates, aromatase inhibitors, siRNA therapeutics, γ -secretase inhibitors, agents that interfere with receptor tyrosine kinases (RTKs) and agents that interfere with cell cycle checkpoints.

In one embodiment, the anti-cancer agent is selected from the group consisting of
35 abarelix (Plenaxis depot®); aldesleukin (Prokine®); Aldesleukin (Proleukin®); Alemtuzumab (Campath®); alitretinoin (Panretin®); allopurinol (Zyloprim®); altretamine (Hexalen®); amifostine (Ethyol®); anastrozole (Arimidex®); arsenic trioxide (Trisenox®); asparaginase

(Elspar®); azacitidine (Vidaza®); bevacuzimab (Avastin®); bexarotene capsules (Targretin®); bexarotene gel (Targretin®); bleomycin (Blenoxane®); bortezomib (Velcade®); busulfan intravenous (Busulfex®); busulfan oral (Myleran®); calusterone (Methosarb®); capecitabine (Xeloda®); carboplatin (Paraplatin®); carmustine (BCNU®, BiCNU®); carmustine (Gliadel®);

5 carmustine with Polifeprosan 20 Implant (Gliadel Wafer®); celecoxib (Celebrex®); cetuximab (Erbix®); chlorambucil (Leukeran®); cisplatin (Platinol®); cladribine (Leustatin®, 2-CdA®); clofarabine (Clolar®); cyclophosphamide (Cytosan®, Neosar®); cyclophosphamide (Cytosan Injection®); cyclophosphamide (Cytosan Tablet®); cytarabine (Cytosar-U®); cytarabine liposomal (DepoCyt®); dacarbazine (DTIC-Dome®); dactinomycin, actinomycin D

10 (Cosmegen®); Darbepoetin alfa (Aranesp®); daunorubicin liposomal (DanuoXome®); daunorubicin, daunomycin (Daunorubicin®); daunorubicin, daunomycin (Cerubidine®); Denileukin diftitox (Ontak®); dexrazoxane (Zinecard®); docetaxel (Taxotere®); doxorubicin (Adriamycin PFS®); doxorubicin (Adriamycin®, Rubex®); doxorubicin (Adriamycin PFS Injection®); doxorubicin liposomal (Doxil®); dromostanolone propionate (dromostanolone®);

15 dromostanolone propionate (masterone injection®); Elliott's B Solution (Elliott's B Solution®); epirubicin (Ellence®); Epoetin alfa (epogen®); erlotinib (Tarceva®); estramustine (Emcyt®); etoposide phosphate (Etopophos®); etoposide, VP-16 (Vepesid®); exemestane (Aromasin®); Filgrastim (Neupogen®); floxuridine (intraarterial) (FUDR®); fludarabine (Fludara®); fluorouracil, 5-FU (Adrucil®); fulvestrant (Faslodex®); gefitinib (Iressa®); gemcitabine

20 (Gemzar®); gemtuzumab ozogamicin (Mylotarg®); goserelin acetate (Zoladex Implant®); goserelin acetate (Zoladex®); histrelin acetate (Histrelin implant®); hydroxyurea (Hydrea®); Ibritumomab Tiuxetan (Zevalin®); idarubicin (Idamycin®); ifosfamide (IFEX®); imatinib mesylate (Gleevec®); interferon alfa 2a (Roferon A®); Interferon alfa-2b (Intron A®); irinotecan (Camptosar®); lenalidomide (Revlimid®); letrozole (Femara®); leucovorin

25 (Wellcovorin®, Leucovorin®); Leuprolide Acetate (Eligard®); levamisole (Ergamisol®); lomustine, CCNU (CeeBU®); meclorethamine, nitrogen mustard (Mustargen®); megestrol acetate (Megace®); melphalan, L-PAM (Alkeran®); mercaptopurine, 6-MP (Purinethol®); mesna (Mesnex®); mesna (Mesnex tabs®); methotrexate (Methotrexate®); methoxsalen (Uvadex®); mitomycin C (Mutamycin®); mitotane (Lysodren®); mitoxantrone (Novantrone®);

30 nandrolone phenpropionate (Durabolin-50®); nelarabine (Arranon®); Nofetumomab (Verluma®); Oprelvekin (Neumega®); oxaliplatin (Eloxatin®); paclitaxel (Paxene®); paclitaxel (Taxol®); paclitaxel protein-bound particles (Abraxane®); palifermin (Kepivance®); pamidronate (Aredia®); pegademase (Adagen (Pegademase Bovine)®); pegaspargase (Oncaspar®); Pegfilgrastim (Neulasta®); pemetrexed disodium (Alimta®); pentostatin

35 (Nipent®); pipobroman (Vercyte®); plicamycin, mithramycin (Mithracin®); porfimer sodium (Photofrin®); procarbazine (Matulane®); quinacrine (Atabrine®); Rasburicase (Elitek®); Rituximab (Rituxan®); sargramostim (Leukine®); Sargramostim (Prokine®); sorafenib

(Nexavar®); streptozocin (Zanosar®); sunitinib maleate (Sutent®); talc (Sclerosol®); tamoxifen (Nolvadex®); temozolomide (Temodar®); teniposide, VM-26 (Vumon®); testolactone (Teslac®); thioguanine, 6-TG (Thioguanine®); thiotepa (Thioplex®); topotecan (Hycamtin®); toremifene (Fareston®); Tositumomab (Bexxar®); Tositumomab/I-131 tositumomab (Bexxar®);
5 Trastuzumab (Herceptin®); tretinoin, ATRA (Vesanoid®); Uracil Mustard (Uracil Mustard Capsules®); valrubicin (Valstar®); vinblastine (Velban®); vincristine (Oncovin®); vinorelbine (Navelbine®); zoledronate (Zometa®) and vorinostat (Zolinza®); a pharmaceutically acceptable salt thereof, and a mixture thereof.

The term "administration" and variants thereof (e.g., "administering" a
10 compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other
15 agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

20 The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

Further included within the scope of the invention is a method for treating an
25 inflammatory disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of the instant invention.

Further included within the scope of the invention is a method for treating an inflammatory disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of the instant invention wherein the
30 inflammatory disease is selected from rheumatoid arthritis, inflammatory bowel disease and cancer.

The compounds of the instant invention are useful for the treatment and/or reducing the severity of rheumatoid arthritis.

35 The compounds of the instant invention are useful for the treatment and/or reducing the severity of inflammatory bowel disease.

The compounds of the instant invention are useful for the treatment and/or reducing the severity of lupus.

The compounds of the instant invention are useful for the treatment and/or reducing the severity of cancer.

The compounds of the instant invention are useful for the treatment of rheumatoid arthritis.

5 The compounds of the instant invention are useful for the treatment of inflammatory bowel disease.

The compounds of the instant invention are useful for the treatment of lupus.

The compounds of the instant invention are useful for the treatment of cancer.

10 Further included within the scope of the invention is a method of treating an inflammatory disease which comprises administering a therapeutically effective amount of a compound of the instant invention in combination with a second therapeutic agent.

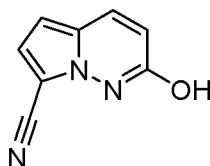
15 Further included within the scope of the invention is a method of treating an inflammatory disease which comprises administering a therapeutically effective amount of a compound of the instant invention in combination with a second therapeutic agent, wherein the second therapeutic agent is selected from an anti-cancer agent and an anti-inflammatory agent.

Abbreviations used in the description of the chemistry and in the Examples that follow are: Ac (Acetyl); ACN or MeCN (acetonitrile); AcOH or HOAc (acetic acid); Boc or BOC (*tert*-butoxycarbonyl); Bu (butyl); Bz (benzoyl); calc'd (calculated); Cbz (benzylloxycarbonyl); CDCl₃ (chloroform-d); CHCl₃ (Chloroform); DAST ((diethylamino)sulfur trifluoride); DCM (dichloromethane); DIEA or Hünig's base (N,N-diisopropylethylamine); DMAP (4-dimethylaminopyridine); DMSO (Dimethylsulfoxide); DMF (dimethylformamide); dppf (1,1'-bis(diphenylphosphino)ferrocene); Et (ethyl); EtOH (ethanol); EtOAc (ethyl acetate); g (grams); GST (glutathione S-transferase); h (hour); HATU (N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate); HCl (hydrochloric acid); HOBt (1-hydroxybenzotriazole); HPLC (high-performance liquid chromatography); IPA or iPrOH (isopropanol); iPr (isopropyl); LC (liquid chromatography); LCMS (liquid chromatography mass spectrometry); M (molar); mCPBA (m-chloroperoxybenzoic acid); Me (methyl); MeOH (methanol); mg (milligrams); min (minute); μL (microliters); mL (milliliters); mmol (millimoles); MS (mass spectrometry); MTBE (methyl *tert*-butyl ether); NMR (nuclear magnetic resonance spectroscopy); OAc (Acetate); Pd(dppf)Cl₂ (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium(II)); Ph (phenyl); POCl₃ (phosphorous oxychloride); Pr (propyl); rac (racemic mixture); RT or rt (room temperature (ambient, about 25 °C)); sat (saturated); SFC (supercritical fluid chromatography); tBu (*tert*-butyl); TEA (triethylamine (Et₃N)); TFA (trifluoroacetic acid); THF (tetrahydrofuran); TLC (thin layer chromatography); and Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene).

General Synopsis of Reaction Schemes

amines. Alternatively, intermediates **G** are chlorinated with POCl₃ and coupled with an array of amines to afford compounds **H**.

INTERMEDIATE 1

2-Hydroxypyrrolo[1,2-*b*]pyridazine-7-carbonitrile

Step 1: A mixture of 3-methoxypyridazine (12.0 mL, 130 mmol) and oxirane-2,2,3,3-tetracyanitrile (20 g, 140 mmol) in THF (240 mL) was stirred at 0 °C for 2 h and at 4 °C for 40 h. The reaction was concentrated to afford crude dicyano(3-methoxypyridazin-1-ium-1-yl)methanide as a solid, which was taken to the next step without further purification. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 8.56 (d, *J* = 6.0 Hz, 1H), 7.94 (m, 1H), 7.14 (d, *J* = 9.2 Hz, 1H), 3.97 (s, 3H).

Step 2: A mixture of the crude dicyano(3-methoxypyridazin-1-ium-1-yl)methanide (21 g, 120 mmol) and ethyne-1,2-diylbis(trimethylsilane) (272 mL, 120 mmol) in toluene (200 mL) was stirred under reflux for 3 d. The reaction mixture was cooled to room temperature, diluted with EtOAc (200 mL), filtered and washed with EtOAc. The filtrate was concentrated and purified by column chromatography to afford a mixture of 2-methoxy-5,6-bis(trimethylsilyl)pyrrolo[1,2-*b*]pyridazine-7-carbonitrile and 2-methoxy-6-(trimethylsilyl)pyrrolo[1,2-*b*]pyridazine-7-carbonitrile as a solid.

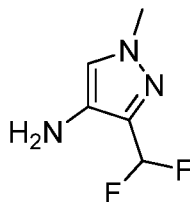
Step 3: To a solution of 2-methoxy-5,6-bis(trimethylsilyl)pyrrolo[1,2-*b*]pyridazine-7-carbonitrile and 2-methoxy-6-(trimethylsilyl)pyrrolo[1,2-*b*]pyridazine-7-carbonitrile (28 g) in THF (200 mL) was added TBAF (132 mL, 132 mmol) at 0 °C and the resulting reaction mixture was stirred at room temperature overnight. The mixture was treated with water, concentrated, diluted with EtOAc (500 mL) and washed with water (200 mL) and brine (200 mL). The aqueous layer was extracted with EtOAc (200 mL x 2). The combined organic layers were dried over Na₂SO₄, concentrated and purified by column chromatography to afford 2-methoxypyrrolo[1,2-*b*]pyridazine-7-carbonitrile as a solid.

Step 4: To a solution of 2-methoxypyrrolo[1,2-*b*]pyridazine-7-carbonitrile (14.0 g, 81.0 mmol) in CH₂Cl₂ (250 mL) was added AlCl₃ (16.0 g, 122 mmol) at room temperature and the reaction was stirred at 45 °C for 24 h. The reaction mixture was cooled to room temperature, treated with Rochelle salt and extracted with EtOAc (200 mL). The organic layer was washed with brine

(100 mL), dried over Na₂SO₄, concentrated and purified by column chromatography on silica gel to afford 2-hydroxypyrrolo[1,2-*b*]pyridazine-7-carbonitrile as a solid. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 12.03 (brs, 1H), 8.05 (d, *J* = 9.6 Hz, 1H), 7.34 (d, *J* = 4.8 Hz, 1H), 6.65 (d, *J* = 9.6 Hz, 1H), 6.58 (d, *J* = 4.8 Hz, 1H). MS [M+H]⁺ calc'd 160, found 160.

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INTERMEDIATE 2



10 3-(Difluoromethyl)-1-methyl-1H-pyrazol-4-amine

Step 1: Into a 100 mL round bottom flask containing a solution of methyl 1-methyl-4-nitro-1*H*-pyrazole-3-carboxylate (1.5 g, 8 mmol) in dichloromethane (30 mL) was added diisobutylaluminum hydride (12 mL, 1 M in toluene, 12 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was treated with hydrochloric acid (1.5 N, 1 mL) and extracted with ethyl acetate. The organic fraction was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with methanol in dichloromethane (5-10%) to yield (1-methyl-4-nitro-1*H*-pyrazol-3-yl)methanol as a solid. ¹H NMR (DMSO-*d*₆, 300 MHz): δ 8.77 (s, 1H), 5.19 (t, *J* = 5.9 Hz, 1H), 4.63 (d, *J* = 5.9 Hz, 2H), 3.85 (s, 3H).

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Step 2: Into a 50 mL round bottom flask containing a solution of 2-iodoxybenzoic acid (2.8 g, 10 mmol) in dimethyl sulfoxide (3 mL) was added a solution of (1-methyl-4-nitro-1*H*-pyrazol-3-yl)methanol (800 mg, 5 mmol) in dimethyl sulfoxide (3 mL) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with diethyl ether and washed with water and brine. The organic fraction was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with methanol in dichloromethane to yield 1-methyl-4-nitro-1*H*-pyrazole-3-carbaldehyde as a solid. ¹H NMR (CDCl₃, 400 MHz): δ 10.43 (s, 1H), 8.25 (s, 1H), 4.09 (s, 3H).

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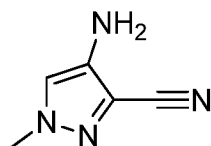
Step 3: Into a 25 mL round bottom flask containing a solution of 1-methyl-4-nitro-1*H*-pyrazole-3-carbaldehyde (300 mg, 1.9 mmol) in dichloromethane (5 mL) was added diethylaminosulfur trifluoride (0.76 mL, 5.8 mmol) at -20 °C and the reaction was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography eluting with methanol in dichloromethane (3-5%) to yield 3-

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(difluoromethyl)-1-methyl-4-nitro-1*H*-pyrazole. ¹H NMR (CDCl₃, 400 MHz): δ 8.19 (s, 1H), 7.13 (t, *J* = 53.2 Hz, 1H), 4.03 (s, 3H).

Step 4: Into a 25 mL round bottom flask containing a solution of 3-(difluoromethyl)-1-methyl-4-nitro-1*H*-pyrazole (300 mg, 1.93 mmol) in methanol (3 mL) was added palladium on carbon (15 mg, 5% w/w) and the reaction was stirred at room temperature for 8 h under hydrogen bladder pressure. The reaction mixture was filtered through celite and washed with methanol and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with methanol in dichloromethane (4-7%) to yield 3-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-amine. ¹H NMR (CDCl₃, 400 MHz): δ 7.09 (s, 1H), 6.86 (t, *J* = 54.1 Hz, 1H), 3.70 (s, 3H). MS calc'd [M+H]⁺ 148.1, found 148.2.

INTERMEDIATE 3



4-Amino-1-methyl-1*H*-pyrazole-3-carbonitrile

Step 1: Into a 250 mL round bottom flask containing a suspension of 4-nitro-1*H*-pyrazole-3-carboxylic acid (20.0 g, 127 mmol) in methanol (100 mL) was added concentrated sulfuric acid (4 mL) dropwise over 5 min at 0 °C and the resulting slurry was refluxed at 80 °C for 16 h. The solvent was removed under reduced pressure and the residual mass was dissolved in ethyl acetate (300 mL) and washed with saturated aqueous sodium bicarbonate solution (2 x 100 mL) and brine (100 mL) and dried over anhydrous sodium sulfate. The solution was filtered and concentrated under reduced pressure to give methyl 4-nitro-1*H*-pyrazole-3-carboxylate as a solid. The crude product was taken to the next step without further purification. MS calc'd [M-H]⁺ 170.0, found 170.0.

Step 2: Into a 1 L round bottom flask containing a suspension of sodium hydride (60% in paraffin oil, 4.7 g, 116 mmol) in tetrahydrofuran (400 mL) at 0 °C was added methyl 4-nitro-1*H*-pyrazole-3-carboxylate (16.5 g, 96 mmol) in tetrahydrofuran (50 mL) dropwise and the reaction mixture was stirred for 1 h. To the reaction mixture was added methyl iodide (9 mL, 145 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was cooled to 0 °C and treated with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (4 x 200 mL). The combined organic fractions were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with ethyl acetate in petroleum ether (15-25%) to

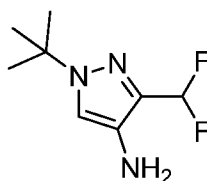
afford methyl 1-methyl-4-nitro-1*H*-pyrazole-3-carboxylate as a solid. ¹H NMR (CDCl₃, 400 MHz): δ 8.17 (s, 1H), 4.03 (s, 3H), 4.01 (s, 3H).

Step 3: Into a 250 mL sealed tube were added methyl 1-methyl-4-nitro-1*H*-pyrazole-3-carboxylate (2.5 g, 13.5 mmol) and methanol (60 mL) and the reaction mixture was cooled to -60 °C and ammonia gas was purged for 15 min and then heated at 80 °C for 4 h. The reaction mixture was cooled to -15 °C and the excess ammonia gas was carefully removed by bubbling nitrogen and concentrated under reduced pressure to afford 1-methyl-4-nitro-1*H*-pyrazole-3-carboxamide as a solid. ¹H NMR (CD₃OD, 300 MHz): δ 8.56 (s, 1H), 3.94 (s, 3H). MS calc'd [M+H]⁺ 171.0, found 171.2.

Step 4: Into a 250 mL sealed tube containing a solution of 1-methyl-4-nitro-1*H*-pyrazole-3-carboxamide (2.0 g, 12 mmol) in dichloromethane (100 mL) was added *N,N*-diisopropylethylamine (13 mL, 71 mmol) at 0 °C. To this reaction mixture was added phosphorous oxychloride (3.3 mL, 35 mmol) dropwise and the mixture was stirred at room temperature for 1 h. The reaction was treated with saturated sodium bicarbonate solution and extracted with dichloromethane. The combined organics were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with ethyl acetate in petroleum ether (25-30%) to afford 1-methyl-4-nitro-1*H*-pyrazole-3-carbonitrile as a solid. ¹H NMR (CDCl₃, 400 MHz): δ 8.24 (s, 1H), 4.09 (s, 3H).

Step 5: Into a 250 mL round bottom flask containing a solution of 1-methyl-4-nitro-1*H*-pyrazole-3-carbonitrile (3.5 g, 23 mmol) in methanol (100 mL) at room temperature was added palladium on carbon (0.5 g, 15% w/w) and the reaction mixture was stirred at room temperature under hydrogen bladder atmosphere for 2 h. The reaction mixture was filtered through celite and washed with methanol and dichloromethane. The filtrate was concentrated under reduced pressure to afford 4-amino-1-methyl-1*H*-pyrazole-3-carbonitrile as a solid. ¹H NMR (CD₃OD, 400 MHz): δ 7.22 (s, 1H), 3.84 (s, 3H). MS calc'd [M+H]⁺ 123.1, found 123.4.

INTERMEDIATE 4



1-(*tert*-Butyl)-3-(difluoromethyl)-1*H*-pyrazol-4-amine

Step 1: Into a 50 mL round bottom flask containing a solution of 4-nitro-1*H*-pyrazole-3-carboxylic acid (5.0 g, 32 mmol) in *tert*-butanol (25 mL) was added sulfuric acid (2 mL, 32 mmol) and the mixture was heated at 100 °C for 16 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and water, and neutralized with saturated solution of sodium bicarbonate. The aqueous layer was extracted with ethyl acetate and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with ethyl acetate in petroleum ether (50-70%) to afford 1-(*tert*-butyl)-4-nitro-1*H*-pyrazole-3-carboxylic acid as a solid. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 13.90 (brs, 1H), 8.96 (s, 1H), 1.55 (s, 9H).

Step 2: Into a 250 mL round bottom flask containing a suspension of 1-(*tert*-butyl)-4-nitro-1*H*-pyrazole-3-carboxylic acid (2.0 g, 11 mmol) in methanol (50 mL) was added concentrated sulfuric acid (0.5 mL) dropwise at 0 °C and the reaction mixture was heated at 80 °C for 16 h. The solvent was removed under reduced pressure and the residual mixture was dissolved in ethyl acetate (50 mL), washed with saturated aqueous sodium bicarbonate (2 x 10 mL) and brine and dried over anhydrous sodium sulfate. The solution was filtered and concentrated under reduced pressure to give methyl 1-(*tert*-butyl)-4-nitro-1*H*-pyrazole-3-carboxylate as a solid. The crude product was taken to the next step without further purification. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 9.05 (s, 1H), 3.89 (s, 3H), 1.57 (s, 9H).

Step 3: Into a 100 mL round bottom flask containing a solution of 1-(*tert*-butyl)-4-nitro-1*H*-pyrazole-3-carboxylate (1.7 g, 10 mmol) in dichloromethane (50 mL) was added diisobutylaluminum hydride (15 mL, 1 M in toluene, 15 mmol) at 0 °C and the reaction was stirred at room temperature for 6 h. The reaction mixture was treated with saturated ammonium chloride solution. The precipitated solid was filtered through celite and the filtrate was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to yield 1-(*tert*-butyl)-4-nitro-1*H*-pyrazol-3-yl)methanol as a solid. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 8.83 (s, 1H), 5.18 (t, *J* = 5.6 Hz, 1H), 4.66 (d, *J* = 5.6 Hz, 2H), 1.55 (s, 9H).

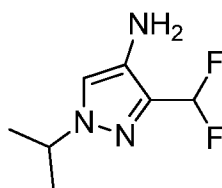
Step 4: Into a 100 mL round bottom flask containing a solution of 2-iodoxybenzoic acid (1.7 g, 6 mmol) in dimethyl sulfoxide (40 mL) was added a solution of 1-(*tert*-butyl)-4-nitro-1*H*-pyrazol-3-yl)methanol (600 mg, 3 mmol) in dimethyl sulfoxide (10 mL) and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with diethyl ether, washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with ethyl acetate in petroleum ether (20-30%) to yield 1-(*tert*-butyl)-4-nitro-1*H*-pyrazole-3-carbaldehyde as a solid. ¹H NMR (CDCl₃, 400 MHz): δ 10.43 (s, 1H), 8.32 (s, 1H), 1.68 (s, 9H).

Step 5: Into a 50 mL round bottom flask containing a solution of 1-(*tert*-butyl)-4-nitro-1*H*-pyrazole-3-carbaldehyde (300 mg, 1.5 mmol) in dichloromethane (20 mL) was added

diethylaminosulfur trifluoride (0.7 mL, 6 mmol) at -20 °C and the mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography eluting with ethyl acetate in petroleum ether (10-20%) to yield 1-(*tert*-butyl)-3-(difluoromethyl)-4-nitro-1*H*-pyrazole. ¹H NMR (CDCl₃, 400 MHz): δ 8.30 (s, 1H), 7.12 (t, *J* = 53.6 Hz, 1H), 1.66 (s, 9H).

Step 6: Into a 50 mL round bottom flask containing a solution of 1-(*tert*-butyl)-3-(difluoromethyl)-4-nitro-1*H*-pyrazole (250 mg, 1.1 mmol) in methanol (15 mL) was added palladium on carbon (25 mg, 10% w/w) and the reaction was stirred at room temperature for 8 h under hydrogen bladder pressure. The reaction mixture was filtered through celite and washed with methanol and the filtrate was concentrated under reduced pressure to afford 1-(*tert*-butyl)-3-(difluoromethyl)-1*H*-pyrazol-4-amine. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 7.21 (s, 1H), 6.88 (t, *J* = 54.4 Hz, 1H), 4.07 (brs, 2H), 1.44 (s, 9H).

INTERMEDIATE 5



3-(Difluoromethyl)-1-isopropyl-1*H*-pyrazol-4-amine

Step 1: Into a 100 mL round bottom flask containing a solution of methyl 4-nitro-1*H*-pyrazole-3-carboxylate (5.0 g, 29 mmol) in dimethylformamide (50 mL) were added anhydrous potassium carbonate (8.0 g, 58 mmol) and 2-iodopropane (5.8 mL, 58 mmol) at 0 °C and the mixture was stirred at room temperature for 16 h. The reaction mixture was filtered through celite and washed with ethyl acetate. The filtrate was washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified flash chromatography eluting with ethyl acetate in petroleum ether (10-20%) to afford a mixture of regioisomers, methyl 1-isopropyl-4-nitro-1*H*-pyrazole-5-carboxylate (2.2 g, 35% yield) as a colorless oil and methyl 1-isopropyl-4-nitro-1*H*-pyrazole-3-carboxylate as an oil. For methyl 1-isopropyl-4-nitro-1*H*-pyrazole-5-carboxylate; ¹H NMR (CD₃OD, 400 MHz): δ 8.16 (s, 1H), 4.75-4.71 (m, 1H), 4.04 (s, 3H), 1.52 (d, *J* = 6.6 Hz, 6H). For methyl 1-isopropyl-4-nitro-1*H*-pyrazole-3-carboxylate; ¹H NMR (CD₃OD, 400 MHz): δ 8.68 (s, 1H), 4.66-4.59 (m, 1H), 3.95 (s, 3H), 1.55 (d, *J* = 6.7 Hz, 6H).

Step 2: Into a 250 mL round bottom flask containing a solution of methyl 1-isopropyl-4-nitro-1*H*-pyrazole-3-carboxylate (4.6 g, 22 mmol) in dichloromethane (50 mL) was added

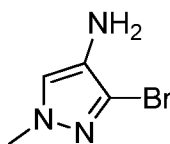
diisobutylaluminum hydride (1M solution in toluene, 32 mL, 32 mmol) at 0 °C and the mixture was stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C, treated with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (2 x 200 mL). The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure and purified by flash chromatography eluting with ethyl acetate in petroleum ether (20-30%) to afford (1-isopropyl-4-nitro-1*H*-pyrazol-3-yl)methanol as an oil. ¹H NMR (CD₃OD, 400 MHz): δ 8.60 (s, 1H), 4.88 (d, *J* = 13.2 Hz, 2H), 4.58-4.55 (m, 1H), 1.54 (d, *J* = 6.8 Hz, 6H). MS calc'd [M+H]⁺ 186.1, found 186.2.

Step 3: Into a 100 mL round bottom flask containing a solution of 2-iodoxybenzoic acid (6.7 g, 24 mmol) in dimethyl sulfoxide (60 mL) was added (1-isopropyl-4-nitro-1*H*-pyrazol-3-yl)methanol (2.2 g, 12 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was treated with water (200 mL) and extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with ethyl acetate in petroleum ether (30-50%) to afford 1-isopropyl-4-nitro-1*H*-pyrazole-3-carbaldehyde.

Step 4: Into a 50 mL round bottom flask containing a solution of 1-isopropyl-4-nitro-1*H*-pyrazole-3-carbaldehyde (1.5 g, 8 mmol) in dichloromethane (20 mL) was added diethylaminosulfur trifluoride (3.3 mL, 25 mmol) at -30 °C and the reaction mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was diluted with dichloromethane (20 mL) and washed with saturated sodium bicarbonate solution, water and brine solution. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography eluting with ethyl acetate in petroleum ether (20-30%) to afford 3-(difluoromethyl)-1-isopropyl-4-nitro-1*H*-pyrazole as an oil. ¹H NMR (CD₃OD, 400 MHz): δ 8.74 (s, 1H), 7.16 (t, *J* = 53.6 Hz, 1H), 4.68-4.61 (m, 1H), 1.56 (d, *J* = 6.8 Hz, 6H).

Step 5: Into a 50 mL round bottom flask containing a solution of 3-(difluoromethyl)-1-isopropyl-4-nitro-1*H*-pyrazole (1.3 g, 6.3 mmol) in methanol (25 mL) was added palladium on carbon (330 mg, 25% w/w) and the reaction mixture was stirred under hydrogen atmosphere for 16 h. The reaction mixture was filtered through celite and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to afford 3-(difluoromethyl)-1-isopropyl-1*H*-pyrazol-4-amine as an oil. MS calc'd [M+H]⁺ 176.1, found 176.4.

INTERMEDIATE 6

3-Bromo-1-methyl-1*H*-pyrazol-4-amine

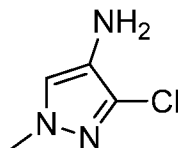
- 5 Step 1: Into a 250 mL round bottom flask containing a solution of 3-amino-1-methyl-1*H*-pyrazole (5.0 g, 52 mmol) in dichloromethane (100 mL) at 0 °C was added triethylamine (18 mL, 129 mmol). After 10 min, trifluoroacetic anhydride (9.5 mL, 67 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with dichloromethane (50 mL), washed with water and brine, dried over anhydrous sodium sulfate,
- 10 filtered and concentrated under reduced pressure to afford 2,2,2-trifluoro-*N*-(1-methyl-1*H*-pyrazol-3-yl)acetamide as a solid. ¹H NMR (CDCl₃, 400 MHz): δ 9.26 (brs, 1H), 7.33 (d, *J* = 2.2 Hz, 1H), 6.73 (d, *J* = 2.2 Hz, 1H), 3.84 (s, 3H). MS calc'd [M+H]⁺ 194.1, found 194.4.
- Step 2: Into a 100 mL round bottom flask containing a solution of 2,2,2-trifluoro-*N*-(1-methyl-1*H*-pyrazol-3-yl)acetamide (8.5 g, 44 mmol) in concentrated sulfuric acid (14 mL) was added
- 15 fuming nitric acid (14 mL) at 0 °C dropwise and the reaction was stirred at room temperature for 2 h. The reaction mixture was treated with ice cold water and extracted with ethyl acetate. The combined organic fractions were washed with saturated sodium bicarbonate solution, water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 2,2,2-trifluoro-*N*-(1-methyl-4-nitro-1*H*-pyrazol-3-yl)acetamide which was taken to the
- 20 next step without further purification. ¹H NMR (CDCl₃, 300 MHz): δ 9.86 (s, 1H), 8.15 (s, 1H), 3.98 (s, 3H). MS calc'd [M-H]⁺ 237.0, found 237.0.
- Step 3: Into a 500 mL round bottom flask containing a solution of 2,2,2-trifluoro-*N*-(1-methyl-4-nitro-1*H*-pyrazol-3-yl)acetamide (8.5 g, 36 mmol) in methanol (200 mL) and water (50 mL) was added potassium carbonate (12.5 g, 89 mmol) and the reaction was stirred at room temperature
- 25 for 24 h. The mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate (150 mL), washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography eluting with ethyl acetate to afford 1-methyl-4-nitro-1*H*-pyrazol-3-amine as a solid. ¹H NMR (DMSO-*d*₆, 300 MHz): δ 8.44 (s, 1H), 6.22 (s, 2H), 3.65 (s, 3H). MS calc'd
- 30 [M+H]⁺ 143.1, found 143.2.
- Step 4: Into a 250 mL round bottom flask containing a solution of copper(II) bromide (3.0 g, 14 mmol) and *tert*-butyl nitrite (1.7 mL, 14 mmol) in acetonitrile (150 mL) was added 1-methyl-4-nitro-1*H*-pyrazol-3-amine (2 g, 14 mmol) in acetonitrile (20 mL) at 0 °C and the reaction was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced
- 35 pressure. The residue was dissolved in ethyl acetate (120 mL), washed with water and brine,

dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography eluting with ethyl acetate in petroleum ether (20-30%) to afford 3-bromo-1-methyl-4-nitro-1*H*-pyrazole as a solid. ¹H NMR (CDCl₃, 300 MHz): δ 8.25 (s, 1H), 3.89 (s, 3H).

- 5 Step 5: Into a 100 mL round bottom flask containing a solution of 3-bromo-1-methyl-4-nitro-1*H*-pyrazole (1.0 g) in ethyl acetate (50 mL) at room temperature was added Raney Nickel (700 mg) and the reaction mixture was stirred at room temperature for 16 h under hydrogen atmosphere. The reaction mixture was filtered through celite and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and purified by flash chromatography eluting
10 with ethyl acetate in petroleum ether (40-50%) to afford 3-bromo-1-methyl-1*H*-pyrazol-4-amine as a liquid. ¹H NMR (CD₃OD, 400 MHz): δ 7.18 (s, 1H), 3.77 (s, 3H). MS calc'd [M+H]⁺ 176.0, found 176.2.

INTERMEDIATE 7

15



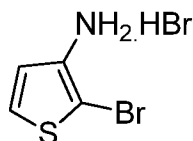
3-Chloro-1-methyl-1*H*-pyrazol-4-amine

- 20 Step 1: Into a 250 mL round bottom flask containing a solution of 1-methyl-4-nitro-1*H*-pyrazol-3-amine (4.0 g, 28 mmol) in acetonitrile (100 mL) was added concentrated hydrochloric acid (8 mL) dropwise at 0 °C. To this reaction mixture was added sodium nitrite (8.0 g, 116 mmol) in portions and the reaction mixture was gradually brought to room temperature and stirred for 16 h. The reaction mixture was cooled to 0 °C, treated with water (30 mL) and extracted with ethyl
25 acetate (2x50 mL). The combined organics were washed with saturated sodium bicarbonate solution, water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography eluting with ethyl acetate in petroleum ether (20-30%) to furnish 3-chloro-1-methyl-4-nitro-1*H*-pyrazole as a solid. ¹H NMR (CDCl₃, 300 MHz): δ 8.25 (s, 1H), 3.98 (s, 3H).
- 30 Step 2: Into a 100 mL round bottom flask containing a solution of 3-chloro-1-methyl-4-nitro-1*H*-pyrazole (2.0 g) in ethyl acetate (50 mL) was added Raney Ni (1.0 g) and the reaction mixture was stirred under hydrogen atmosphere for 24 h. The reaction mixture was filtered through celite and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and purified by flash chromatography eluting with ethyl acetate in petroleum ether (40-

50%) to afford 3-chloro-1-methyl-1*H*-pyrazol-4-amine as an oil. ¹H NMR (CD₃OD, 400 MHz): δ 7.17 (s, 1H), 3.73 (s, 3H).

INTERMEDIATE 8

5



2-Bromo-3-aminothiophene hydrobromide

10 Step 1: Into a 100 mL round bottom flask containing a solution of thiophene-3-carboxylic acid (4.0 g, 31 mmol) in toluene (40 mL) were added diphenylphosphoryl azide (9.5 g, 34 mmol) and *N,N*-diisopropylethylamine (6.7 mL, 38 mmol) at 0 °C and the reaction was stirred at room temperature for 1 h. The reaction mixture was cooled to 0 °C, treated with *tert*-butanol (12 mL, 124 mmol) and heated to 120 °C for 5 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography eluting with ethyl acetate in petroleum ether (2-5%) to afford *tert*-butyl thiophen-3-ylcarbamate as a solid. ¹H NMR (CDCl₃, 400 MHz): δ 7.23-7.21 (m, 2H), 6.93 (d, *J* = 5.6 Hz, 1H), 6.71 (brs, 1H), 1.54 (s, 9H).

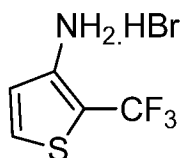
Step 2: Into a 100 mL round bottom flask containing a solution of *tert*-butyl thiophen-3-ylcarbamate (4.2 g, 21 mmol) in carbon tetrachloride (40 mL) was added *N*-bromosuccinimide (7.5 g, 42 mmol) and the reaction mixture was heated at 80 °C for 2 h. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with ethyl acetate in petroleum ether (2-5%) to afford *tert*-butyl (2-bromothiophen-3-yl)carbamate as a solid. ¹H NMR (CDCl₃, 400 MHz): δ 7.59 (d, *J* = 3.3 Hz, 1H), 7.26 (d, *J* = 3.4 Hz, 1H), 6.58 (brs, 1H), 1.54 (s, 9H). MS calc'd [M+H]⁺ 278.0, found 278.2.

Step 3: Into a 10 mL round bottom flask containing a solution of *tert*-butyl (2-bromothiophen-3-yl)carbamate (500 mg) in dichloromethane (5 mL) was added HBr in acetic acid (0.5 mL) dropwise at 0 °C and reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and triturated using diethyl ether to afford 2-bromothiophen-3-amine hydrobromide as a solid. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 7.66 (d, *J* = 5.8 Hz, 1H), 6.96 (d, *J* = 5.8 Hz, 1H).

The following intermediate was prepared in an analogous manner of that described in Intermediate 8.

Intermediate #	Structure	IUPAC Name	Exact Mass [M+H] ⁺
9		2-chlorothiophen-3-amine hydrochloride	Calc'd 134.0, found 134.4

INTERMEDIATE 10

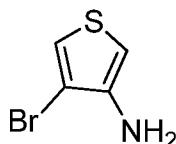


2-(Trifluoromethyl)thiophen-3-amine hydrobromide

Step 1: Into a 50 mL round bottom flask containing a solution of *tert*-butyl thiophen-3-ylcarbamate (1.0 g, 5 mmol) in *tert*-butanol (30 mL) were added 1-(trifluoromethyl)-1³,2-benziodoxol-3(1*H*)-one (3.3 g, 10 mmol) and copper(I) chloride (100 mg, 1 mmol) and the reaction was heated at 115 °C for 8 h. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with saturated sodium bicarbonate solution, water and brine. The solution was dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure and purified by flash column chromatography eluting with ethyl acetate in petroleum ether (15-20%) to furnish *tert*-butyl (2-(trifluoromethyl)thiophen-3-yl)carbamate as a solid. ¹H NMR (CDCl₃, 300 MHz): δ 7.77 (d, *J* = 4.4 Hz, 1H), 7.38 (d, *J* = 5.5 Hz, 1H), 6.91 (brs, 1H), 1.53 (s, 9H).

Step 2: Into a 25 mL round bottom flask *tert*-butyl (2-(trifluoromethyl)thiophen-3-yl)carbamate (800 mg) in dichloromethane (10 mL) was added HBr in acetic acid (1 mL) at 0 °C and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and triturated using diethyl ether to afford 2-(trifluoromethyl)thiophen-3-amine hydrobromide as a solid. ¹H NMR (DMSO-*d*₆, 300 MHz): δ 7.51 (d, *J* = 5.2 Hz, 1H), 6.59 (d, *J* = 4.0 Hz, 1H).

INTERMEDIATE 11

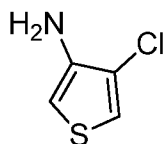


4-Bromo-3-aminothiophene

Step 1: Into a 100 mL round bottom flask containing a solution of 3,4-dibromothiophene (5.0 g, 21 mmol) in toluene (50 mL) were added benzophenone imine (4.1 g, 23 mmol), palladium acetate (140 mg, 0.6 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (510 mg, 0.83 mmol) and cesium carbonate (13.4 g, 41 mmol) and the reaction mixture was degassed for 15 min using nitrogen gas and heated at 110 °C for 16 h. The reaction mixture was filtered through celite and washed with ethyl acetate. The filtrate was concentrated under reduced pressure and purified by flash column chromatography eluting with ethyl acetate in petroleum ether (2-5%) to afford *N*-(4-bromothiophen-3-yl)-1,1-diphenylmethanimine as a solid. ¹H NMR (CDCl₃, 400 MHz): δ 7.85-7.82 (m, 3H), 7.64-7.60 (m, 2H), 7.53-7.49 (m, 3H), 7.45-7.42 (m, 1H), 7.39-7.36 (m, 2H), 7.23-7.18 (m, 1H). MS calc'd [M+H]⁺ 342.0, found 342.0.

Step 2: Into a 50 mL round bottom flask containing a solution of *N*-(4-bromothiophen-3-yl)-1,1-diphenylmethanimine (4.0 g, 12 mmol) in dichloromethane (20 mL) was added hydrochloric acid (4 M solution in 1,4-dioxane, 10 mL) at 0 °C and the reaction was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure, triturated using diethyl ether and dried under high vacuum to afford 4-bromothiophen-3-amine hydrochloride as a solid. ¹H NMR (CDCl₃, 400 MHz): δ 7.15 (d, *J* = 3.6 Hz, 1H), 6.25 (d, *J* = 3.6 Hz, 1H). MS calc'd [M+H]⁺ 177.9, found 178.2.

INTERMEDIATE 12



4-Chlorothiophen-3-amine

Step 1: Into a 250 mL round bottom flask containing a solution of methyl 4-aminothiophene-3-carboxylate (2.5 g, 16 mmol) in concentrated hydrochloric acid (21 mL) was added sodium nitrite (1.2 g, 18 mmol) in water (5 mL) dropwise at 0 °C and the reaction mixture was stirred for 1 h. The mixture was treated with copper(I) chloride (2.5 g, 19 mmol) in chloroform (25 mL) and heated at 50 °C for 16 h. The reaction mixture was cooled to room temperature, treated with saturated sodium carbonate solution and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with ethyl acetate in petroleum ether (0-4%) to furnish methyl 4-

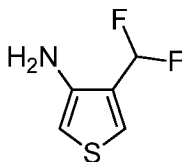
chlorothiophene-3-carboxylate as a liquid. ^1H NMR (CDCl_3 , 400 MHz): δ 8.13 (d, $J = 3.7$ Hz, 1H), 7.20 (d, $J = 3.7$ Hz, 1H), 3.90 (s, 3H).

Step 2: Into a 25 mL round bottom flask containing a solution of methyl 4-chlorothiophene-3-carboxylate (600 mg, 3.4 mmol) in tetrahydrofuran (6 mL) and water (1 mL) was added lithium hydroxide monohydrate (240 mg, 10 mmol) and the reaction was stirred at room temperature for 16 h. The mixture was concentrated under reduced pressure and acidified to pH 2 using diluted hydrochloric acid (1.5 N). The reaction mixture was extracted with ethyl acetate. The combined organic fractions were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 4-chlorothiophene-3-carboxylic acid as a liquid. ^1H NMR (CDCl_3 , 300 MHz): δ 8.29 (d, $J = 3.7$ Hz, 1H), 6.57 (d, $J = 3.6$ Hz, 1H). MS calc'd $[\text{M-H}]^+$ 161.0, found 161.0.

Step 3: Into a 100 mL round bottom flask containing a solution of 4-chlorothiophene-3-carboxylic acid (500 mg, 3 mmol) in toluene (20 mL) were added diphenylphosphoryl azide (2.5 g, 3.4 mmol) and *N,N*-diisopropylethylamine (0.7 mL, 3.7 mmol) and the reaction was stirred at room temperature for 1 h. To this mixture was added *tert*-butanol (1.2 mL, 12 mmol) and the mixture was heated at 100 °C for 3 h. The reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate (120 mL), washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography eluting with ethyl acetate in petroleum ether (2-4%) to furnish *tert*-butyl (4-chlorothiophen-3-yl)carbamate as a solid. ^1H NMR (CDCl_3 , 400 MHz): δ 7.53 (d, $J = 4.8$ Hz, 1H), 7.11 (d, $J = 3.6$ Hz, 1H), 6.82 (brs, 1H), 1.43 (s, 9H). MS calc'd $[\text{M-Boc+H}]^+$ 134.0, found 134.4.

Step 4: Into a 10 mL round bottom flask containing a solution of *tert*-butyl (4-chlorothiophen-3-yl)carbamate (400 mg, 1.7 mmol) in dichloromethane (4 mL) was added hydrochloric acid solution (4M solution in 1,4-dioxane, 0.3 mL) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, triturated with diethyl ether and dried under high vacuum to afford 4-chlorothiophen-3-amine hydrochloride as a solid. ^1H NMR (CD_3OD , 400 MHz): δ 7.64 (s, 2H). MS calc'd $[\text{M+H}]^+$ 134.0, found 134.4.

INTERMEDIATE 13



4-(Difluoromethyl)thiophen-3-amine

Step 1: Into a 100 mL round bottom flask containing a solution of 3,4-dibromothiophene (4.0 g, 17 mmol) in diethyl ether (50 mL) was added *n*-butyl lithium in hexane (1 M solution in hexanes, 17 mL, 17 mmol) at -78 °C over 15 min. To this mixture was added *N,N*-

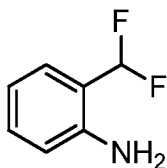
5 dimethylformamide and the reaction was stirred for 3 h. The reaction mixture was treated with saturated ammonium chloride solution and extracted with diethyl ether (2 x 50 mL). The combined organics were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to furnish 4-bromothiophene-3-carbaldehyde as a liquid which was directly taken to the next step without further purification. ¹H NMR (CDCl₃, 400 MHz): δ 9.99 (s, 1H), 8.17 (s, 1H), 7.76 (s, 1H).

Step 2: Into a 50 mL round bottom flask containing a solution of 4-bromothiophene-3-carbaldehyde (3.5 g, 18 mmol) in dichloromethane (40 mL) was added diethylaminosulfur trifluoride (7.3 mL, 55 mmol) at 0 °C and the reaction was stirred at room temperature for 16 h. The reaction mixture was diluted with dichloromethane (20 mL) and washed with saturated sodium bicarbonate solution, water and brine. The solution was dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure and purified by flash column chromatography eluting with ethyl acetate in petroleum ether (2-5%) to furnish 3-bromo-4-(difluoromethyl)thiophene as a liquid. ¹H NMR (CDCl₃, 300 MHz): δ 7.68 (s, 1H), 7.35 (s, 1H), 6.67 (t, *J* = 55.1 Hz, 1H).

Step 3: A solution of 3-bromo-4-(difluoromethyl)thiophene (800 mg, 4 mmol) in *N,N*-dimethylformamide (10 mL) at 0 °C was purged with ammonia gas for 1 h. To this mixture were added potassium phosphate tribasic (2.4 g, 11 mmol) and copper(II) acetylacetonate (300 mg, 1.9 mmol) and the reaction mixture was heated at 90 °C for 16 h. The reaction mixture was diluted with ethyl acetate (20 mL), washed with water and brine, dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure and purified by flash column chromatography eluting with ethyl acetate in petroleum ether (15-20%) to furnish 4-(difluoromethyl)thiophen-3-amine as a liquid. ¹H NMR (CDCl₃, 300 MHz): δ 7.36 (d, *J* = 2.9 Hz, 1H), 6.63 (t, *J* = 55.7 Hz, 1H), 6.24 (d, *J* = 3.3 Hz, 1H). MS calc'd [M+H]⁺ 150.0, found 150.4.

30

INTERMEDIATE 14



2-(Difluoromethyl)aniline hydrobromide

Step 1: Into a 250 mL round bottom flask containing a solution of methyl 2-formylbenzoate (5.0 g, 30 mmol) in dichloromethane (80 mL) were added diethylaminosulfur trifluoride (7 mL, 52 mmol) and methanol (1.5 mL) at -5 °C and the reaction was stirred at room temperature for 16 h.

5 The reaction mixture was diluted with dichloromethane (20 mL) and washed with saturated sodium bicarbonate solution, water and brine. The solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford methyl 2-(difluoromethyl)benzoate as an oil which was taken to the next step without further purification.

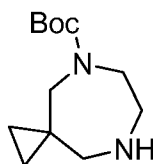
Step 2: Into a 100 mL round bottom flask containing a solution of methyl 2-

10 (difluoromethyl)benzoate (4.3 g, 23 mmol) in tetrahydrofuran (30 mL) and water (15 mL) was added lithium hydroxide monohydrate (2.9 g, 69 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and acidified to pH 2 using diluted hydrochloric acid (1.5 N). The reaction mixture was extracted with ethyl acetate. The combined organics were washed with water and brine, dried
15 over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 2-(difluoromethyl)benzoic acid. The crude product was taken to the next step without further purification. MS calc'd $[M-H]^+$ 171.0, found 171.0.

Step 3: Into a 100 mL round bottom flask containing a solution of 2-(difluoromethyl)benzoic acid (4.0 g, 23 mmol) in toluene (50 mL) were added diphenylphosphoryl azide (5.5 mL, 26 mmol), *N,N*-diisopropylethylamine (5 mL, 28 mmol) and *tert*-butanol (7 mL) and the mixture
20 was stirred at room temperature for 30 min and at 110 °C for 16 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (120 mL), washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography eluting with ethyl
25 acetate in petroleum ether (5-10%) to furnish *tert*-butyl 2-(difluoromethyl)phenylcarbamate as a liquid. ^1H NMR (CDCl_3 , 300 MHz): δ 8.01 (d, J = 8.2 Hz, 1H), 7.49-7.38 (m, 2H), 7.14 (t, J = 7.5 Hz, 1H), 6.86 (brs, 1H), 6.68 (t, J = 55.1 Hz, 1H), 1.53 (s, 9H).

Step 4: Into a 10 mL round bottom flask containing a solution of *tert*-butyl 2-(difluoromethyl)phenylcarbamate (650 mg) in dichloromethane (5 mL) was added HBr in acetic
30 acid (0.5 mL) at 0 °C and the reaction was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, triturated with diethyl ether and dried under high vacuum to afford 2-(difluoromethyl)aniline hydrobromide as a solid. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 7.37-7.35 (m, 1H), 7.32-7.28 (m, 1H), 7.07 (t, J = 55.2 Hz, 1H), 6.95-6.93 (m, 1H), 6.88-6.84 (m, 1H). MS calc'd $[M+H]^+$ 144.1, found 144.4.

INTERMEDIATE 15



tert-Butyl 5,8-diazaspiro[2.6]nonane-5-carboxylate

- 5 Step 1: Into a 5 L 4 necked round bottomed flask was placed a solution of diethyl malonate (300 g, 1.87 mol) and 1,2-dibromoethane (634.5 g, 3.38 mol) in DMSO (1.5 L). The mixture was treated with K_2CO_3 (1020 g, 7.39 mol) and Bu_4NHSO_4 (6.4 g, 19 mmol). The resulting solution was allowed to stir for 48 h at room temperature. The reaction mixture was treated with 2 L of H_2O and extracted with 1.5 L of EtOAc (3x). The organic layers were combined, dried over
- 10 Na_2SO_4 and concentrated under reduced pressure. The residue was distilled under 5-10 mmHg vacuum at 64-65 °C. This resulted in diethyl cyclopropane-1,1-dicarboxylate as an oil.
- Step 2: Into a 100 mL 3 necked round bottomed flask was placed THF (50 mL), then added $LiAlH_4$ (2 g, 53 mmol) in several batches. This was followed by the addition of a solution of diethyl cyclopropane-1,1-dicarboxylate (5 g, 27 mmol) in THF (10 mL) dropwise with stirring,
- 15 while cooling to 0 °C. The resulting solution was allowed to stir for 1 h at 0~5 °C in an ice bath. The reaction mixture was then treated with 2 mL of H_2O , 6 mL of 15% NaOH solution and 2 mL of H_2O . The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was extracted with 50 mL of EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford cyclopropane-1,1-diyl dimethanol as a liquid.
- 20 Step 3: Into a 2 L 3 necked round bottomed flask were placed a solution of cyclopropane-1,1-diyl dimethanol (42 g, 410 mmol) in DCM (200 mL) and DMAP (126 g, 1.03 mol). The mixture was treated with a solution of TsCl (173 g, 907 mmol) in DCM (500 mL) dropwise, while cooling to 0 °C, over 30 min. The resulting solution was allowed to stir for 2.5 h at room temperature. The reaction mixture was washed with H_2O , HCl (1N) and brine, dried over
- 25 Na_2SO_4 and concentrated under reduced pressure. This resulted in cyclopropane-1,1-diyl dimethanediyl bis(4-methylbenzenesulfonate) as a solid.
- Step 4: Into a 5 L 4 necked round bottomed flask was placed a solution of 4-methylbenzene-1-sulfonyl chloride (487 g, 2.55 mol) in ethyl ether (1 L). To the mixture was added a solution of ethane-1,2-diamine (77 g, 1.3 mol) and sodium hydroxide (102 g, 2.55 mol) in H_2O (1 L)
- 30 dropwise while cooled to 0 °C. The resulting solution was allowed to stir for 30 min at 0 °C in an ice bath, then overnight at room temperature. A filtration was performed and the filter cake was washed 2 times with H_2O and dried in an oven. This resulted in (crude) of *N,N'*-ethane-1,2-diylbis(4-methylbenzenesulfonamide) as a solid.
- Into a 5 L 4 necked round bottom flask were placed *N,N'*-ethane-1,2-diylbis(4-
- 35 methylbenzenesulfonamide) (150 g, 408 mmol), cyclopropane-1,1-diyl dimethanediyl bis(4-

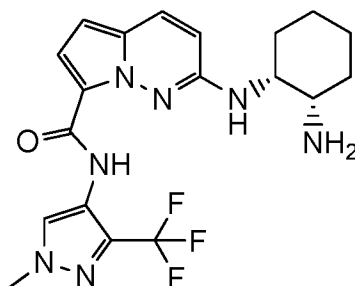
methylbenzenesulfonate) (200 g, 487 mmol), 18-crown-6 (53 g, 200 mmol) and THF (2 L) followed by the addition of a solution of *t*-BuOK (100 g, 893 mmol) in THF (500 mL) dropwise with stirring at -30 °C. The resulting solution was allowed to stir for 2 days at room temperature. The resulting mixture was concentrated under reduced pressure to remove most of THF. The residual solution was diluted with 1500 mL of H₂O. The precipitate was collected by filtration and dried. The residue was purified by eluting through a silica gel column with dichloromethane/petroleum ether (1:10-1:2). This resulted in 5,8-bis[(4-methylphenyl)sulfonyl]-5,8-diazaspiro[2.6]nonane as a solid.

Step 5: Into a 5 L 4 necked round bottomed flask was placed a solution of 5,8-bis[(4-methylphenyl)sulfonyl]-5,8-diazaspiro[2.6]nonane (100 g, 230 mmol) in MeOH (1500 mL). To the mixture was added magnesium (27.4 g, 1.14 mol) batchwise when the reaction mixture was warmed at 40 °C. The resulting mixture was allowed to stir for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure to remove MeOH. The residue was diluted with 500 mL of EtOAc and filtered. The filtrate was treated with a solution of oxalic acid (23 g, 255 mmol) in Et₂O (500 mL). The precipitate was collected by filtration and dried. This resulted in 5-[(4-methylphenyl)sulfonyl]-5,8-diazaspiro[2.6]nonane ethanedioate as a solid.

Step 6: Into a 2 L 3 necked round bottomed flask was placed a solution of 5-[(4-methylphenyl)sulfonyl]-5,8-diazaspiro[2.6]nonane ethanedioate (50 g, 121.48 mmol, 90%) in DCM (800 mL) and Et₃N (31 g, 310 mmol). To the mixture was added Boc₂O (26 g, 119 mmol) at 0-5 °C. The resulting solution was allowed to stir overnight at room temperature. The reaction mixture was washed with 3x500 mL of H₂O and 1x500 mL of brine. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. This resulted in *tert*-butyl 8-[(4-methylphenyl)sulfonyl]-5,8-diazaspiro[2.6]nonane-5-carboxylate as an oil.

Step 7: Into a 3 L 3 necked round bottomed flask was placed a solution of *tert*-butyl 8-[(4-methylphenyl)sulfonyl]-5,8-diazaspiro[2.6]nonane-5-carboxylate (110 g, 232 mmol, 80%) in MeOH (1800 mL). To the mixture was added Mg (36 g, 1.50 mol) in several batches at 40 °C. The resulting solution was allowed to stir for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was diluted with 1 L of EtOAc and filtered. The filtrate was treated with a solution of oxalic acid in ether to precipitate the product. The solid was collected by filtration and washed 2 times with ether. This resulted in *tert*-butyl 5,8-diazaspiro[2.6]nonane-5-carboxylate ethanedioate as a solid. ¹H-NMR (400 MHz, D₂O): δ 0.71-0.736 (d, *J* = 9.6 Hz, 2H), 0.75-0.78 (d, *J* = 9.6 Hz, 2H), 0.77 (m, 4H), 1.42 (s, 9H), 3.18 (s, 2H), 3.33-3.39 (m, 4H), 3.78 (s, 1H). MS [M+H]⁺ 227.

EXAMPLE 1



2-(((1*R*,2*S*)-2-Aminocyclohexyl)amino)-*N*-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide (IRAK4 IC₅₀ = 5 nM)

5

Step 1: Into a 50 mL round bottom flask containing 2-hydroxypyrrolo[1,2-*b*]pyridazine-7-carbonitrile (2 g, 13 mmol) in ethanol (20 mL) was added sodium hydroxide (8 M solution in water, 20 mL, 160 mmol) and the reaction was heated at 110 °C for 16 h. The reaction mixture was brought to room temperature and the pH was adjusted to 2.0 using 1.5 N hydrochloric acid and stirred for 15 min. The precipitate was filtered, washed with water and dried under reduced pressure to afford 2-hydroxypyrrolo[1,2-*b*]pyridazine-7-carboxylic acid as a solid. ¹H NMR (DMSO-*d*₆, 300 MHz): δ 12.33 (brs, 1H), 11.72 (brs, 1H), 8.01 (d, *J* = 9.5 Hz, 1H), 7.22 (d, *J* = 4.7 Hz, 1H), 6.56 (d, *J* = 9.5 Hz, 1H), 6.52 (d, *J* = 4.7 Hz, 1H). MS calc'd [M-H]⁺ 177.0, found 177.2.

15 Step 2: Into a 25 mL sealed tube containing 2-hydroxypyrrolo[1,2-*b*]pyridazine-7-carboxylic acid (400 mg, 2.3 mmol) in *N,N*-dimethylformamide (4 mL) were added 1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-amine (370 mg, 2.3 mmol), *N,N*-diisopropylethylamine (1.4 g, 11 mmol) and 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (1.3 g, 3.4 mmol) and the reaction was heated at 60 °C for 16 h. The reaction mixture was brought to room temperature, concentrated under reduced pressure, treated with ethyl acetate (5 mL) and water (5 mL) and stirred for 15 min. The precipitate was filtered, washed with petroleum ether/diethyl ether and dried under reduced pressure to afford 2-hydroxy-*N*-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide as a solid. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 11.82 (brs, 1H), 11.09 (s, 1H), 8.39 (s, 1H), 8.10 (d, *J* = 9.5 Hz, 1H), 7.34 (d, *J* = 4.7 Hz, 1H), 6.67 (d, *J* = 9.5 Hz, 1H), 6.64 (d, *J* = 4.7 Hz, 1H), 3.95 (s, 3H). MS [M+H]⁺ 326.7.

Step 3: Into a 5 mL microwave vial containing 2-hydroxy-*N*-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide (70 mg, 0.22 mmol) in *N,N*-dimethylformamide (0.8 mL) were added *N,N*-diisopropylethylamine (97 mg, 0.8 mmol) and *N*-phenyl-bis(trifluoromethanesulfonimide) (84 mg, 0.24 mmol) and the reaction mixture was stirred at room temperature for 1 h. To this mixture was added *tert*-butyl ((1*S*,2*R*)-2-aminocyclohexyl)carbamate (55 mg, 0.26 mmol) in *N,N*-dimethylformamide (0.5 mL) and the

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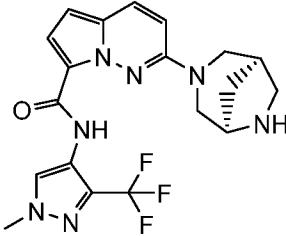
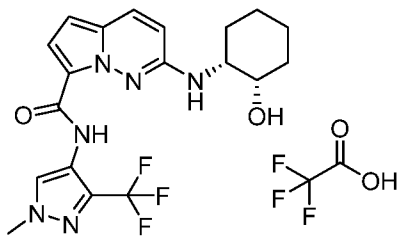
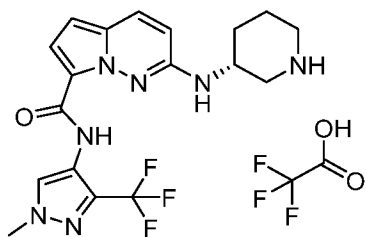
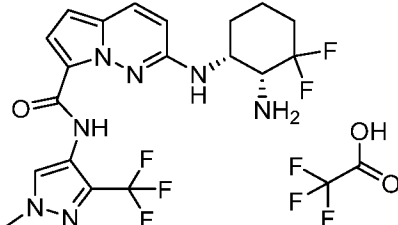
reaction mixture was heated at 110 °C for 3 h. The reaction mixture was brought to room temperature, concentrated under reduced pressure, treated with aqueous ammonium chloride (3 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The solution was filtered,

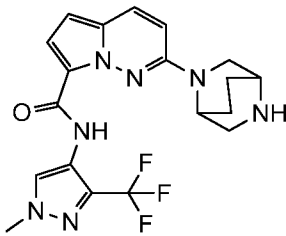
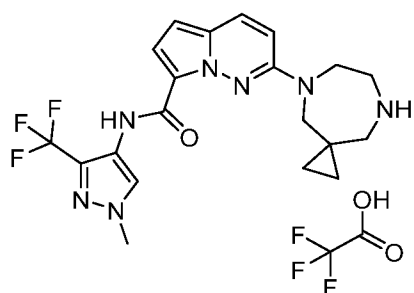
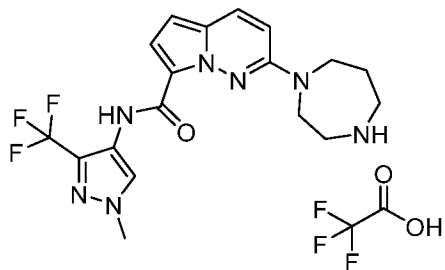
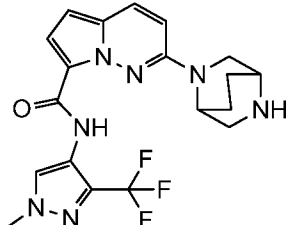
concentrated under reduced pressure and purified by flash chromatography (silica gel) eluting with 30-40% ethyl acetate in petroleum ether to afford *tert*-butyl ((1*S*,2*R*)-2-((7-((1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)carbamoyl)pyrrolo[1,2-*b*]pyridazin-2-yl)amino)cyclohexyl)carbamate as a solid. MS calc'd [M+H]⁺ 522.2, found 522.4.

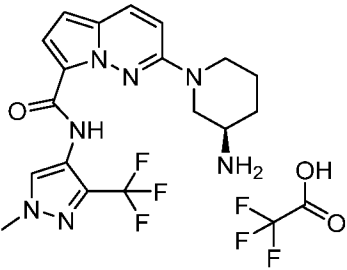
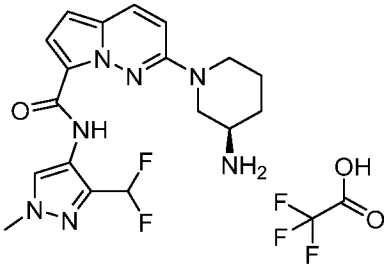
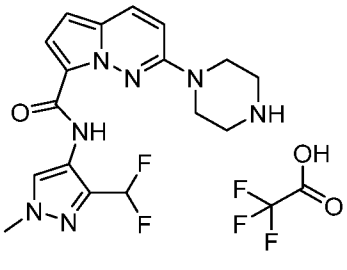
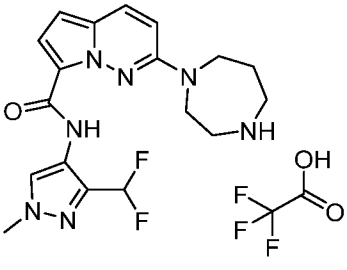
Step 4: A solution of *tert*-butyl ((1*S*,2*R*)-2-((7-((1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)carbamoyl)pyrrolo[1,2-*b*]pyridazin-2-yl)amino)cyclohexyl)carbamate (15 mg) in trifluoroacetic acid (1 mL) was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and purified by preparative HPLC to afford 2-(((1*R*,2*S*)-2-aminocyclohexyl)amino)-*N*-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide trifluoroacetate as a solid. ¹H NMR (CD₃OD, 400 MHz): δ 8.19 (s, 1H), 7.80 (d, *J* = 9.6 Hz, 1H), 7.34 (d, *J* = 4.8 Hz, 1H), 6.66 (d, *J* = 9.6 Hz, 1H), 6.52 (d, *J* = 4.8 Hz, 1H), 4.45 (brs, 1H), 4.00 (s, 3H), 3.58-3.54 (m, 1H), 1.98-1.95 (m, 1H), 1.82-1.69 (m, 7H). MS calc'd [M+H]⁺ 422.2, found 422.2.

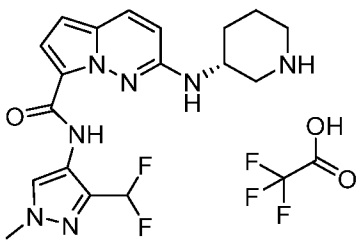
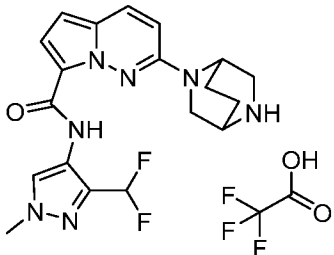
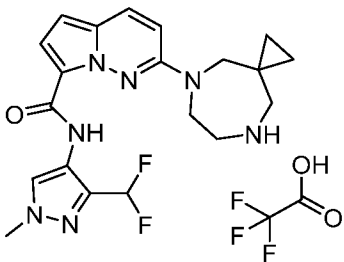
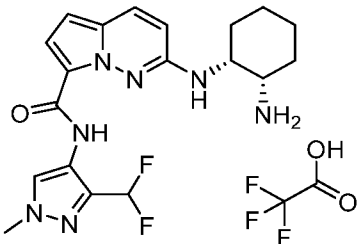
The following examples were prepared in an analogous manner of that described in Example 1.

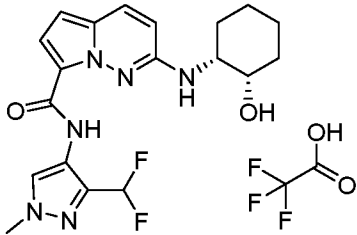
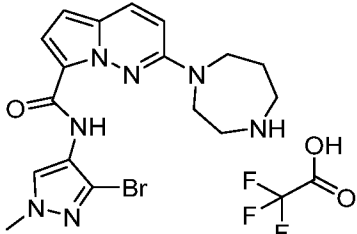
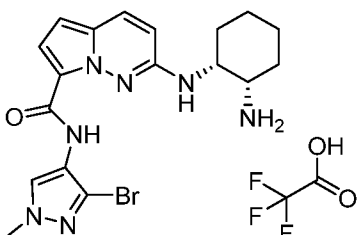
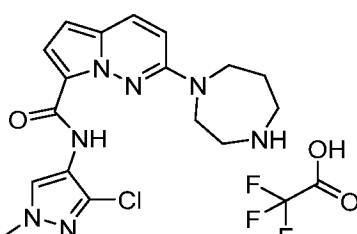
Example #	IRAK4 IC ₅₀ (nM)	Structure	IUPAC Name	Exact Mass [M+H] ⁺
2	ND		2-(3,6-diazabicyclo[3.2.1]oct-3-yl)- <i>N</i> -[1-methyl-3-(trifluoromethyl)-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 420.2, found 420.2
3	85		2-[(1 <i>S</i> ,5 <i>S</i>)- or (1 <i>R</i> ,5 <i>R</i>)-3,6-diazabicyclo[3.2.1]oct-3-yl]- <i>N</i> -[1-methyl-3-(trifluoromethyl)-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 420.2, found 420.2

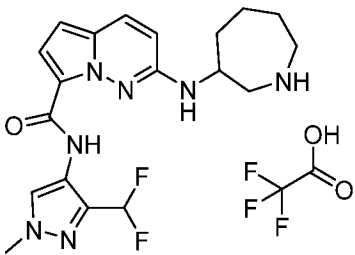
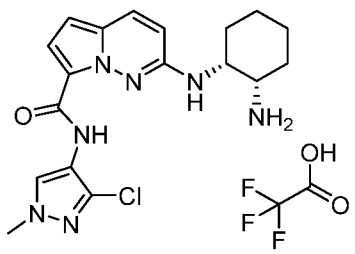
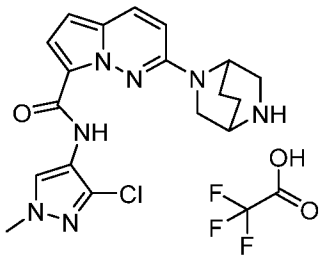
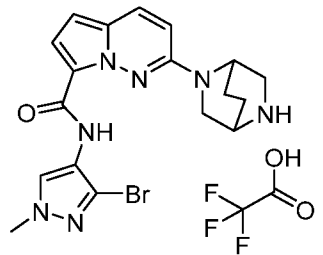
			pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide	
4	131		2-[(1 <i>S</i> ,5 <i>S</i>)- or (1 <i>R</i> ,5 <i>R</i>)-3,6-diazabicyclo[3.2.1]oct-3-yl]- <i>N</i> -[1-methyl-3-(trifluoromethyl)-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide	Calc'd 420.2, found 420.2
5	122		2-[(1 <i>R</i> ,2 <i>S</i>)-2-hydroxycyclohexyl]amino}- <i>N</i> -[1-methyl-3-(trifluoromethyl)-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 423.2, found 423.4
6	1		<i>N</i> -[1-methyl-3-(trifluoromethyl)-1 <i>H</i> -pyrazol-4-yl]-2-[(3 <i>R</i>)-piperidin-3-ylamino]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 408.2, found 408.4
7	189		2-[(1 <i>R</i> ,2 <i>R</i>)-2-amino-3,3-difluorocyclohexyl]amino}- <i>N</i> -[1-methyl-3-(trifluoromethyl)-1 <i>H</i> -	Calc'd 458.2, found 458.4

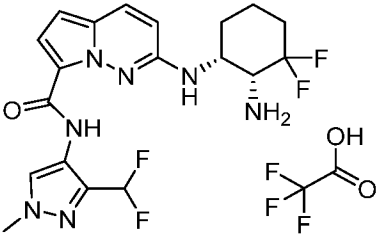
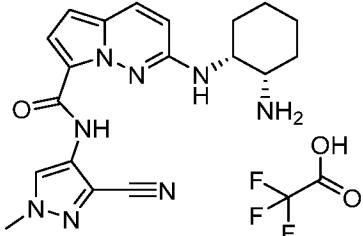
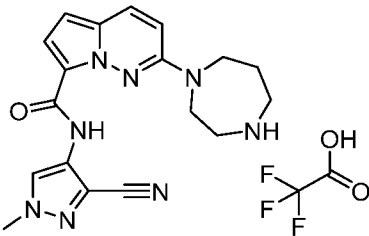
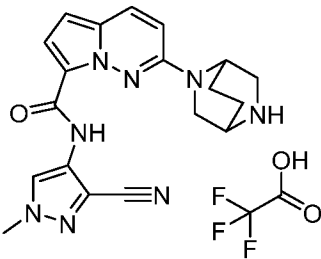
			pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	
8	19		2-(2,5-diazabicyclo[2.2.2]oct-2-yl)- <i>N</i> -[1-methyl-3-(trifluoromethyl)]-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide	Calc'd 420.2, found 420.4
9	27		2-(5,8-diazaspiro[2.6]non-5-yl)- <i>N</i> -[1-methyl-3-(trifluoromethyl)]-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 434.2, found 434.4
10	33		2-(1,4-diazepan-1-yl)- <i>N</i> -[1-methyl-3-(trifluoromethyl)]-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 408.2, found 408.4
11	27		2-(2,5-diazabicyclo[2.2.2]oct-2-yl)- <i>N</i> -[1-methyl-3-(trifluoromethyl)]-1 <i>H</i> -pyrazol-4-	Calc'd 420.2, found 420.4

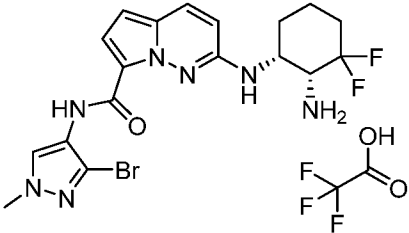
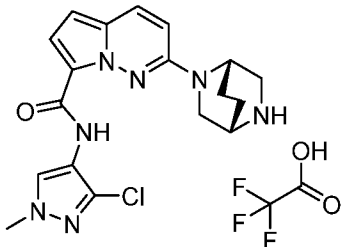
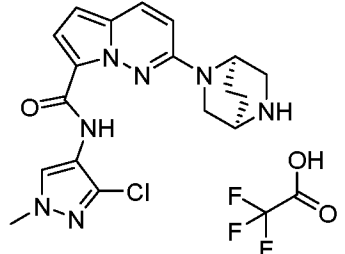
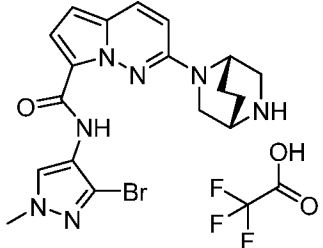
			yl]pyrrolo[1,2- <i>b</i>]pyridazine-7- carboxamide	
12	0.5		2-[(3 <i>R</i>)-3- aminopiperidin-1-yl]- <i>N</i> - [1-methyl-3- (trifluoromethyl)-1 <i>H</i> - pyrazol-4- yl]pyrrolo[1,2- <i>b</i>]pyridazine-7- carboxamide trifluoroacetate	Calc'd 408.2, found 408.6
13	0.5		2-[(3 <i>R</i>)-3- aminopiperidin-1-yl]- <i>N</i> - [3-(difluoromethyl)-1- methyl-1 <i>H</i> -pyrazol-4- yl]pyrrolo[1,2- <i>b</i>]pyridazine-7- carboxamide trifluoroacetate	Calc'd 390.2, found 390.4
14	2		<i>N</i> -[3-(difluoromethyl)- 1-methyl-1 <i>H</i> -pyrazol-4- yl]-2-piperazin-1- ylpyrrolo[1,2- <i>b</i>]pyridazine-7- carboxamide trifluoroacetate	Calc'd 376.2, found 376.4
15	2		2-(1,4-diazepan-1-yl)- <i>N</i> -[3-(difluoromethyl)- 1-methyl-1 <i>H</i> -pyrazol-4- yl]pyrrolo[1,2- <i>b</i>]pyridazine-7- carboxamide trifluoroacetate	Calc'd 390.2, found 390.2

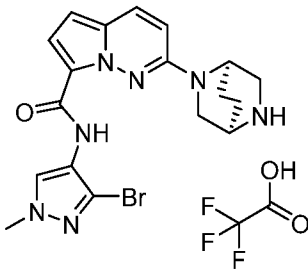
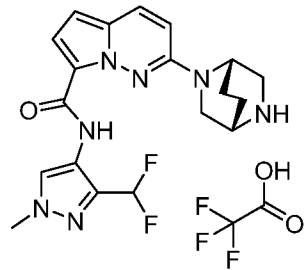
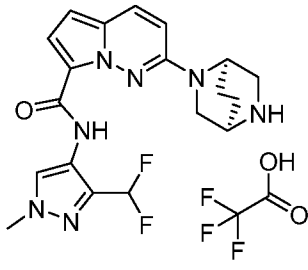
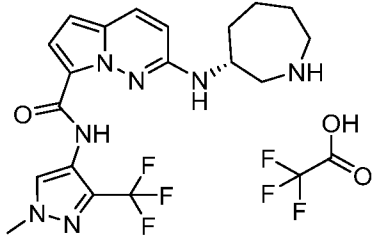
16	0.9		<i>N</i> -[3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]-2-[(3 <i>R</i>)-piperidin-3-ylamino]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 390.2, found 390.4
17	4		2-(2,5-diazabicyclo[2.2.2]oct-2-yl)- <i>N</i> -[3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 402.2, found 402.4
18	2		2-(5,8-diazaspiro[2.6]non-5-yl)- <i>N</i> -[3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 416.2, found 416.4
19	1		2-[(1 <i>R</i> ,2 <i>S</i>)-2-aminocyclohexyl]amino-N-[3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 404.2, found 404.4

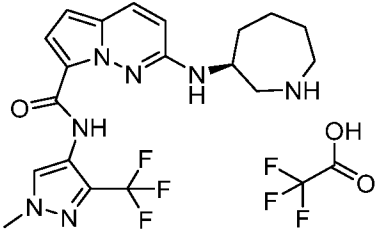
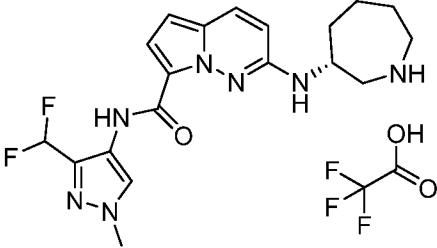
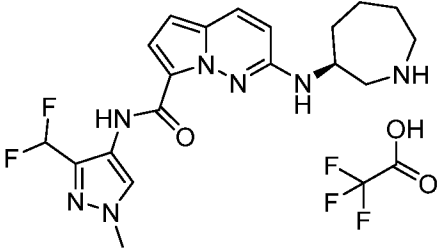
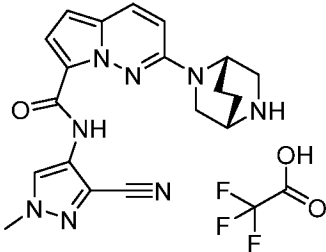
20	11		<i>N</i> -[3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]-2-([(1 <i>R</i> ,2 <i>S</i>)-2-hydroxycyclohexyl]amino)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 405.2, found 405.4
21	32		<i>N</i> -(3-bromo-1-methyl-1 <i>H</i> -pyrazol-4-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 418.1, found 418.4
22	2		2-([(1 <i>R</i> ,2 <i>S</i>)-2-aminocyclohexyl]amino)- <i>N</i> -(3-bromo-1-methyl-1 <i>H</i> -pyrazol-4-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 432.1, found 432.4
23	20		<i>N</i> -(3-chloro-1-methyl-1 <i>H</i> -pyrazol-4-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 374.1, found 374.4

24	2		2-(azepan-3-ylamino)- <i>N</i> -[3-(difluoromethyl)- 1-methyl-1 <i>H</i> -pyrazol-4- yl]pyrrolo[1,2- <i>b</i>]pyridazine-7- carboxamide trifluoroacetate	Calc'd 404.2, found 404.4
25	1		2-{[(1 <i>R</i> ,2 <i>S</i>)-2- aminocyclohexyl]amino }- <i>N</i> -(3-chloro-1-methyl- 1 <i>H</i> -pyrazol-4- yl)pyrrolo[1,2- <i>b</i>]pyridazine-7- carboxamide trifluoroacetate	Calc'd 388.2, found 388.4
26	28		<i>N</i> -(3-chloro-1-methyl- 1 <i>H</i> -pyrazol-4-yl)-2- (2,5- diazabicyclo[2.2.2]oct- 2-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7- carboxamide trifluoroacetate	Calc'd 386.1, found 386.4
27	24		<i>N</i> -(3-bromo-1-methyl- 1 <i>H</i> -pyrazol-4-yl)-2- (2,5- diazabicyclo[2.2.2]oct- 2-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7- carboxamide trifluoroacetate	Calc'd 430.1, found 430.2

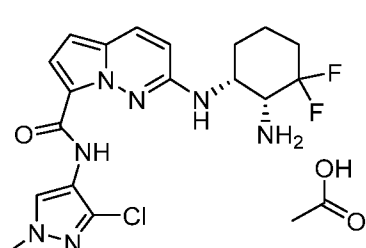
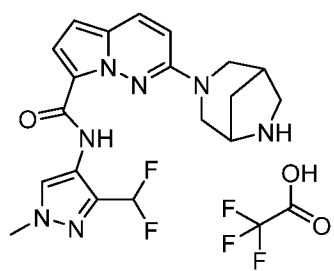
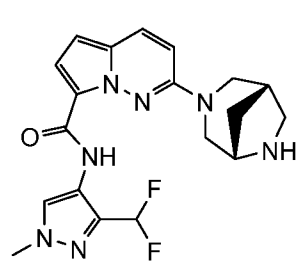
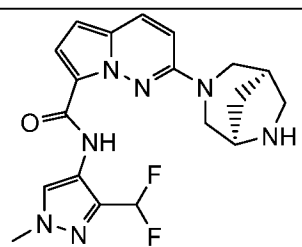
28	34		2-{[(1 <i>R</i> ,2 <i>R</i>)-2-amino-3,3-difluorocyclohexyl]amino}- <i>N</i> -[3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 440.2, found 440.4
29	0.7		2-{[(1 <i>R</i> ,2 <i>S</i>)-2-aminocyclohexyl]amino}- <i>N</i> -(3-cyano-1-methyl-1 <i>H</i> -pyrazol-4-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 379.2, found 379.4
30	27		<i>N</i> -(3-cyano-1-methyl-1 <i>H</i> -pyrazol-4-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 365.2, found 365.2
31	25		<i>N</i> -(3-cyano-1-methyl-1 <i>H</i> -pyrazol-4-yl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 377.2, found 377.4

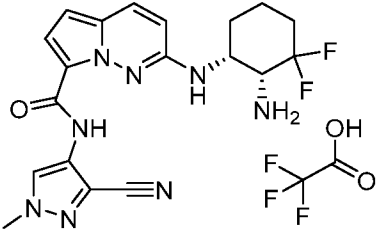
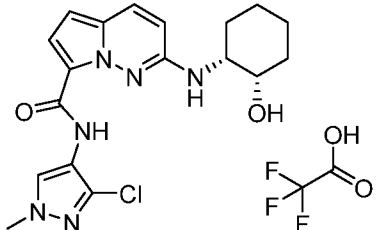
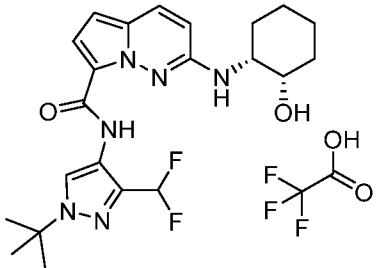
32	275		2-{[(1 <i>R</i> ,2 <i>R</i>)-2-amino-3,3-difluorocyclohexyl]amino}- <i>N</i> -(3-bromo-1-methyl-1 <i>H</i> -pyrazol-4-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 468.1, found 468.2
33	45		<i>N</i> -(3-chloro-1-methyl-1 <i>H</i> -pyrazol-4-yl)-2-[(1 <i>S</i> ,4 <i>S</i>)- or (1 <i>R</i> ,4 <i>R</i>)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 386.1, found 386.4
34	15		<i>N</i> -(3-chloro-1-methyl-1 <i>H</i> -pyrazol-4-yl)-2-[(1 <i>S</i> ,4 <i>S</i>)- or (1 <i>R</i> ,4 <i>R</i>)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 386.1, found 386.4
35	34		<i>N</i> -(3-bromo-1-methyl-1 <i>H</i> -pyrazol-4-yl)-2-[(1 <i>S</i> ,4 <i>S</i>)- or (1 <i>R</i> ,4 <i>R</i>)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide	Calc'd 430.1, found 430.4

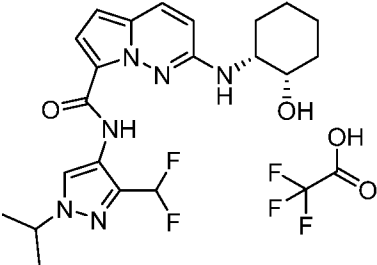
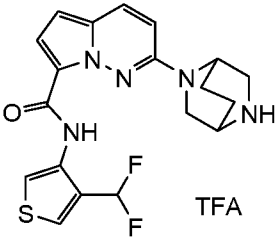
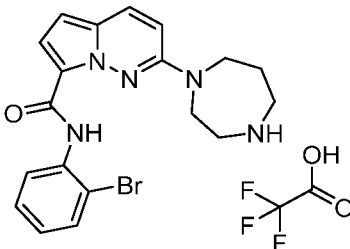
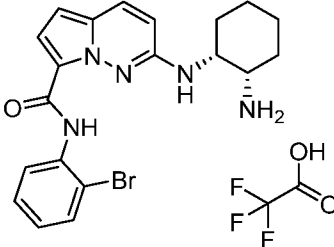
			trifluoroacetate	
36	22		<i>N</i> -(3-bromo-1-methyl-1 <i>H</i> -pyrazol-4-yl)-2-[(1 <i>S</i> ,4 <i>S</i>)- or (1 <i>R</i> ,4 <i>R</i>)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 430.1, found 430.4
37	3		2-[(1 <i>S</i> ,4 <i>S</i>)- or (1 <i>R</i> ,4 <i>R</i>)-2,5-diazabicyclo[2.2.2]oct-2-yl]- <i>N</i> -[3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 402.2, found 402.4
38	2		2-[(1 <i>S</i> ,4 <i>S</i>)- or (1 <i>R</i> ,4 <i>R</i>)-2,5-diazabicyclo[2.2.2]oct-2-yl]- <i>N</i> -[3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 402.2, found 402.4
39	2		2-[(3 <i>R</i>)- or (3 <i>S</i>)-azepan-3-ylamino]- <i>N</i> -[1-methyl-3-(trifluoromethyl)-1 <i>H</i> -pyrazol-4-	Calc'd 422.2, found 422.4

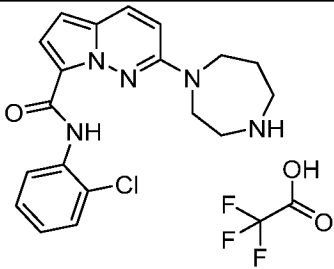
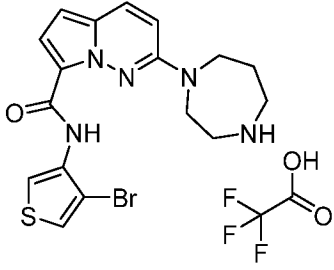
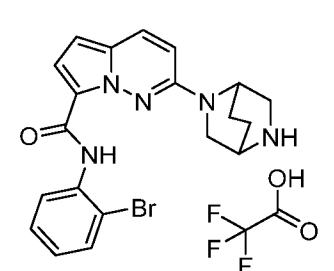
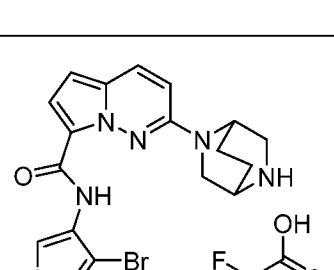
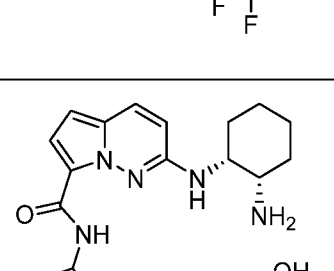
			yl]pyrrolo[1,2- <i>b</i>]pyridazine-7- carboxamide trifluoroacetate	
40	2		2-[(3 <i>R</i>)- or (3 <i>S</i>)-azepan- 3-ylamino]- <i>N</i> -[1- methyl-3- (trifluoromethyl)-1 <i>H</i> - pyrazol-4- yl]pyrrolo[1,2- <i>b</i>]pyridazine-7- carboxamide trifluoroacetate	Calc'd 422.2, found 422.4
41	0.2		2-[(3 <i>R</i>)- or (3 <i>S</i>)-azepan- 3-ylamino]- <i>N</i> -[3- (difluoromethyl)-1- methyl-1 <i>H</i> -pyrazol-4- yl]pyrrolo[1,2- <i>b</i>]pyridazine-7- carboxamide trifluoroacetate	Calc'd 404.2, found 404.4
42	0.3		2-[(3 <i>R</i>)- or (3 <i>S</i>)-azepan- 3-ylamino]- <i>N</i> -[3- (difluoromethyl)-1- methyl-1 <i>H</i> -pyrazol-4- yl]pyrrolo[1,2- <i>b</i>]pyridazine-7- carboxamide trifluoroacetate	Calc'd 404.2, found 404.4
43	25		<i>N</i> -(3-cyano-1-methyl- 1 <i>H</i> -pyrazol-4-yl)-2- [(1 <i>S</i> ,4 <i>S</i>)- or (1 <i>R</i> ,4 <i>R</i>)- 2,5- diazabicyclo[2.2.2]oct- 2-yl]pyrrolo[1,2-	Calc'd 377.2, found 377.4

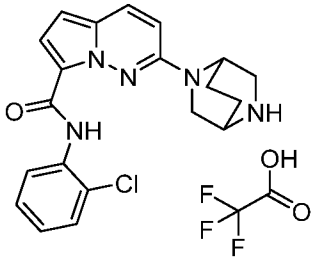
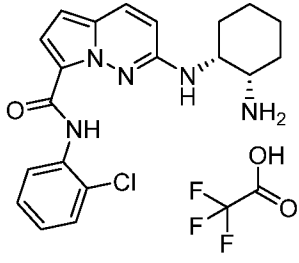
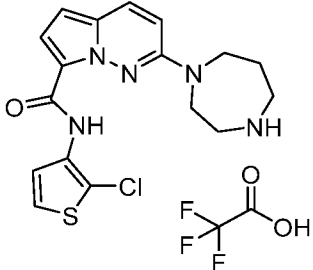
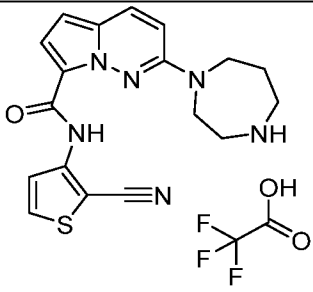
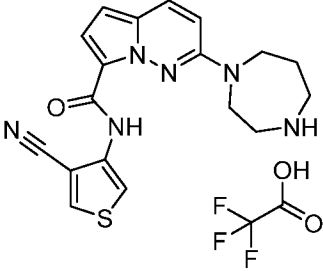
			<i>b</i>]pyridazine-7-carboxamide trifluoroacetate	
44	50		<i>N</i> -(3-cyano-1-methyl-1 <i>H</i> -pyrazol-4-yl)-2-[(1 <i>S</i> ,4 <i>S</i>)- or (1 <i>R</i> ,4 <i>R</i>)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 377.2, found 377.2
45	136		2-[(1 <i>R</i> ,2 <i>S</i>)-2-aminocyclohexyl]amino}- <i>N</i> -[1-methyl-5-(trifluoromethyl)-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 422.2, found 402.4
46	1		2-(3,8-diazabicyclo[3.2.1]oct-3-yl)- <i>N</i> -[3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 402.2, found 402.4
47	9		2-(3,8-diazabicyclo[3.2.1]oct-3-yl)- <i>N</i> -[1-methyl-3-(trifluoromethyl)-1 <i>H</i> -pyrazol-4-	Calc'd 420.2, found 420.4

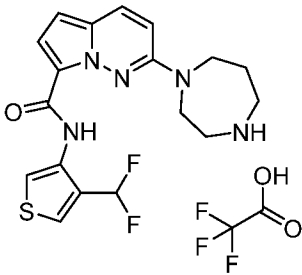
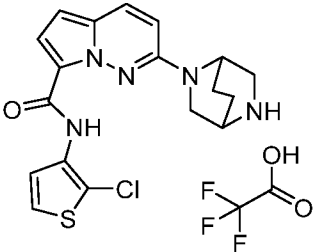
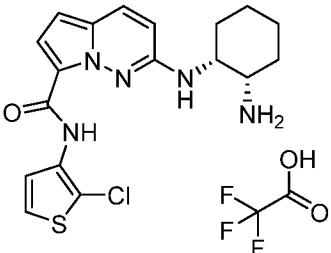
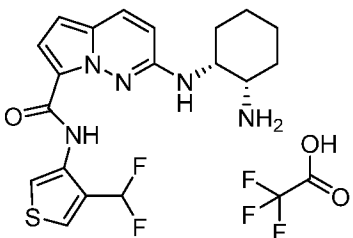
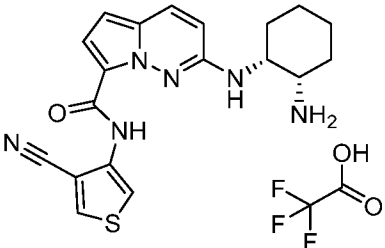
			yl]pyrrolo[1,2- <i>b</i>]pyridazine-7- carboxamide trifluoroacetate	
48	138		2-{[(1 <i>R</i> ,2 <i>R</i>)-2-amino- 3,3- difluorocyclohexyl]ami- no}- <i>N</i> -(3-chloro-1- methyl-1 <i>H</i> -pyrazol-4- yl)pyrrolo[1,2- <i>b</i>]pyridazine-7- carboxamide acetate	Calc'd 424.1, found 424.4
49	ND		2-(3,6- diazabicyclo[3.2.1]oct- 3-yl)- <i>N</i> -[3- (difluoromethyl)-1- methyl-1 <i>H</i> -pyrazol-4- yl]pyrrolo[1,2- <i>b</i>]pyridazine-7- carboxamide trifluoroacetate	Calc'd 402.2, found 402.4
50	4		2-[(1 <i>S</i> ,5 <i>S</i>)- or (1 <i>R</i> ,5 <i>R</i>)- 3,6- diazabicyclo[3.2.1]oct- 3-yl]- <i>N</i> -[3- (difluoromethyl)-1- methyl-1 <i>H</i> -pyrazol-4- yl]pyrrolo[1,2- <i>b</i>]pyridazine-7- carboxamide	Calc'd 402.2, found 402.4
51	12		2-[(1 <i>S</i> ,5 <i>S</i>)- or (1 <i>R</i> ,5 <i>R</i>)- 3,6- diazabicyclo[3.2.1]oct- 3-yl]- <i>N</i> -[3- (difluoromethyl)-1-	Calc'd 402.2, found 402.4

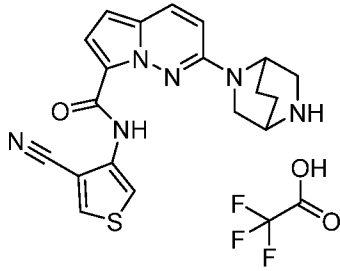
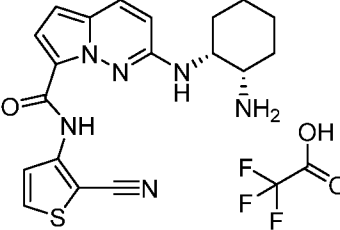
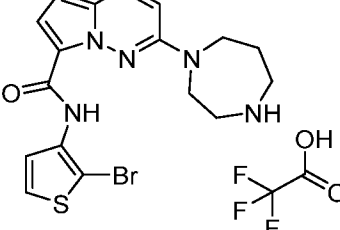
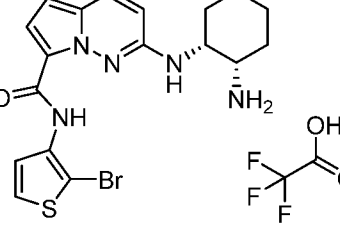
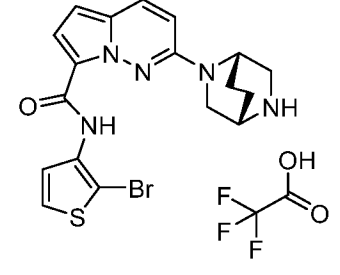
			methyl-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide	
52	43		2-{{(1 <i>R</i> ,2 <i>R</i>)-2-amino-3,3-difluorocyclohexyl}amino}- <i>N</i> -(3-cyano-1-methyl-1 <i>H</i> -pyrazol-4-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 415.2, found 415.2
53	55		<i>N</i> -(3-chloro-1-methyl-1 <i>H</i> -pyrazol-4-yl)-2-{{(1 <i>R</i> ,2 <i>S</i>)-2-hydroxycyclohexyl}amino}pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 389.1, found 389.4
54	640		<i>N</i> -[1-tert-butyl-3-(difluoromethyl)-1 <i>H</i> -pyrazol-4-yl]-2-{{(1 <i>R</i> ,2 <i>S</i>)-2-hydroxycyclohexyl}amino}pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 447.2, found 447.2

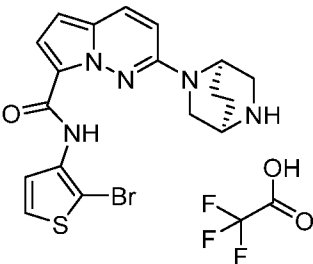
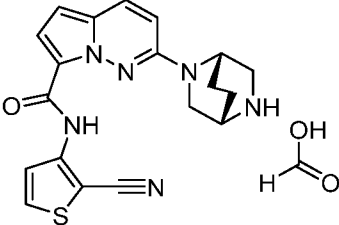
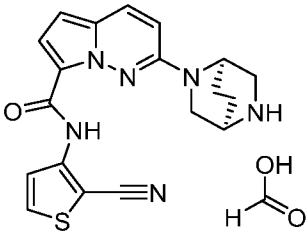
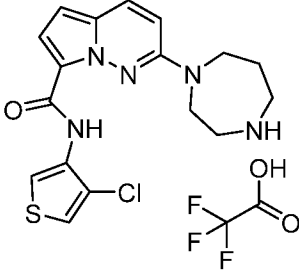
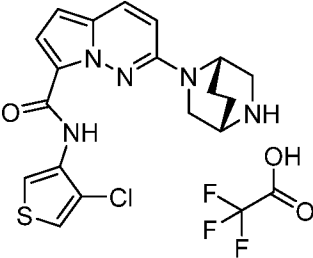
55	53		<i>N</i> -[3-(difluoromethyl)-1-(1-methylethyl)-1 <i>H</i> -pyrazol-4-yl]-2-{{[(1 <i>R</i> ,2 <i>S</i>)-2-hydroxycyclohexyl]amino}pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 433.2, found 433.2
56	95	 TFA	2-(2,5-diazabicyclo[2.2.2]oct-2-yl)- <i>N</i> -[4-(difluoromethyl)thiophen-3-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 404.1, found 404.0
57	3955		<i>N</i> -(2-bromophenyl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 414.1, found 414.4
58	11		2-{{[(1 <i>R</i> ,2 <i>S</i>)-2-aminocyclohexyl]amino}- <i>N</i> -(2-bromophenyl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 428.1, found 428.4

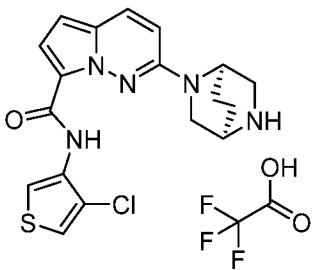
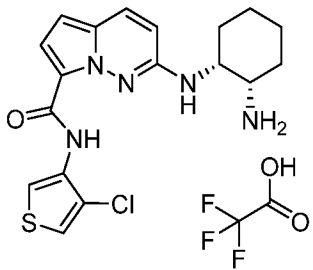
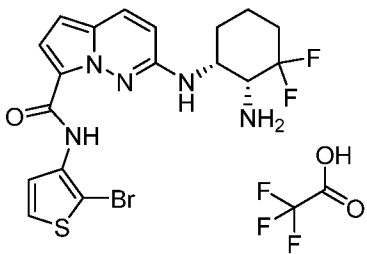
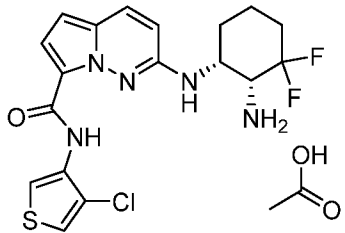
59	1198		<i>N</i> -(2-chlorophenyl)-2-((1,4-diazepan-1-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide) trifluoroacetate	Calc'd 370.1, found 370.4
60	548		<i>N</i> -(4-bromothiophen-3-yl)-2-((1,4-diazepan-1-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide) trifluoroacetate	Calc'd 420.2, found 420.2
61	1665		<i>N</i> -(2-bromophenyl)-2-((2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide) trifluoroacetate	Calc'd 426.1, found 426.4
62	415		<i>N</i> -(4-bromothiophen-3-yl)-2-((2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide) trifluoroacetate	Calc'd 432.1, found 432.1
63	7		2-(((1 <i>R</i> ,2 <i>S</i>)-2-aminocyclohexyl)amino)- <i>N</i> -(4-bromothiophen-3-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 434.2, found 434.2

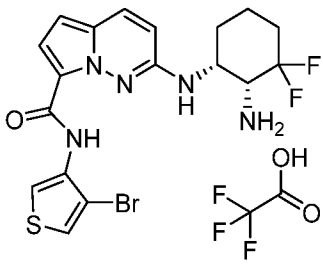
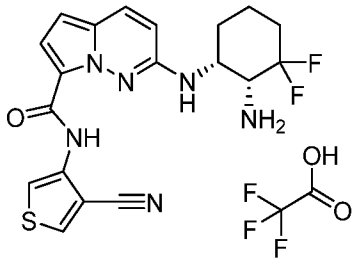
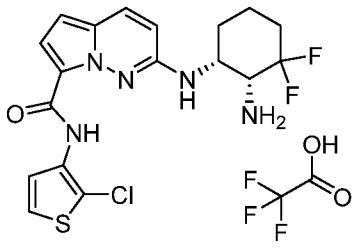
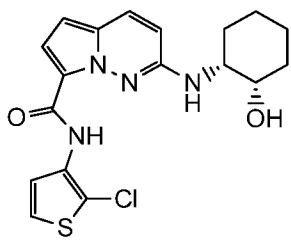
64	611		<i>N</i> -(2-chlorophenyl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 382.1, found 382.2
65	6		2-([(1 <i>R</i> ,2 <i>S</i>)-2-aminocyclohexyl]amino)- <i>N</i> -(2-chlorophenyl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 384.2, found 384.4
66	636		<i>N</i> -(2-chlorothiophen-3-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 376.2, found 376.2
67	197		<i>N</i> -(2-cyanothiophen-3-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 367.1, found 367.4
68	190		<i>N</i> -(4-cyanothiophen-3-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 367.1, found 367.4

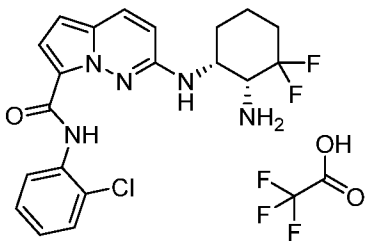
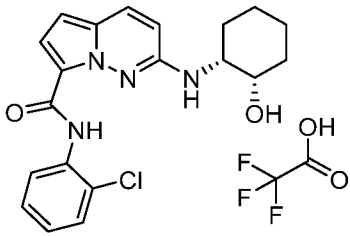
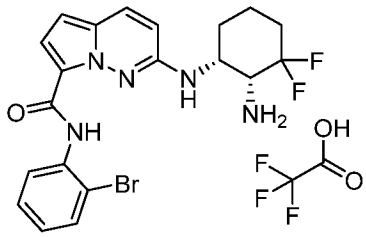
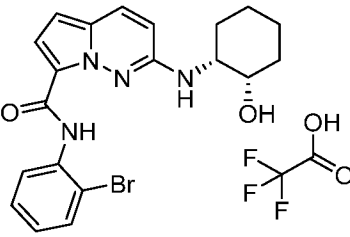
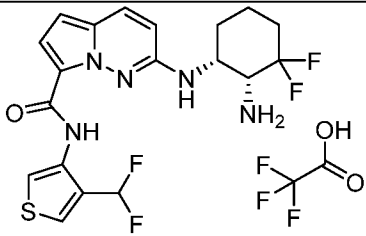
69	151		2-(1,4-diazepan-1-yl)- N-[4-(difluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide trifluoroacetate	Calc'd 392.1, found 392.4
70	433		N-(2-chlorothiophen-3-yl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide trifluoroacetate	Calc'd 388.2, found 388.4
71	4		2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-(2-chlorothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide trifluoroacetate	Calc'd 390.2, found 390.4
72	24		2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-[4-(difluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide trifluoroacetate	Calc'd 406.2, found 406.2
73	3		2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-(4-cyanothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide	Calc'd 381.1, found 381.4

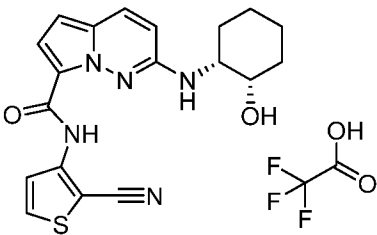
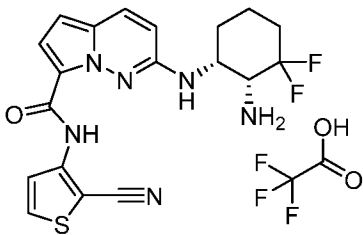
			trifluoroacetate	
74	134		<i>N</i> -(4-cyanothiophen-3-yl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 379.2, found 379.4
75	2		2-([(1 <i>R</i> ,2 <i>S</i>)-2-aminocyclohexyl]amino)- <i>N</i> -(2-cyanothiophen-3-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 381.1, found 381.4
76	1321		<i>N</i> -(2-bromothiophen-3-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 420.2, found 420.2
77	11		2-([(1 <i>R</i> ,2 <i>S</i>)-2-aminocyclohexyl]amino)- <i>N</i> -(2-bromothiophen-3-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 434.2, found 434.4
78	697		<i>N</i> -(2-bromothiophen-3-yl)-2-[(1 <i>S</i> ,4 <i>S</i>)- or (1 <i>R</i> ,4 <i>R</i>)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide	Calc'd 432.1, found 432.4

			trifluoroacetate	
79	192		<i>N</i> -(2-bromothiophen-3-yl)-2-[(1 <i>S</i> ,4 <i>S</i>)- or (1 <i>R</i> ,4 <i>R</i>)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 432.1, found 432.4
80	103		<i>N</i> -(2-cyanothiophen-3-yl)-2-[(1 <i>S</i> ,4 <i>S</i>)- or (1 <i>R</i> ,4 <i>R</i>)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide formate	Calc'd 379.2, found 379.4
81	356		<i>N</i> -(2-cyanothiophen-3-yl)-2-[(1 <i>S</i> ,4 <i>S</i>)- or (1 <i>R</i> ,4 <i>R</i>)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide formate	Calc'd 379.2, found 379.4
82	308		<i>N</i> -(4-chlorothiophen-3-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 376.2, found 376.4
83	188		<i>N</i> -(4-chlorothiophen-3-yl)-2-[(1 <i>S</i> ,4 <i>S</i>)- or (1 <i>R</i> ,4 <i>R</i>)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 388.2, found 388.4

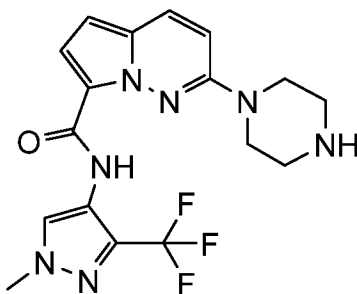
			carboxamide trifluoroacetate	
84	126		<i>N</i> -(4-chlorothiophen-3-yl)-2-[(1 <i>S</i> ,4 <i>S</i>)- or (1 <i>R</i> ,4 <i>R</i>)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 388.2, found 388.4
85	2		2-[(1 <i>R</i> ,2 <i>S</i>)-2-aminocyclohexyl]amino}- <i>N</i> -(4-chlorothiophen-3-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 390.2, found 390.4
86	5244		2-[(1 <i>R</i> ,2 <i>R</i>)-2-amino-3,3-difluorocyclohexyl]amino}- <i>N</i> -(2-bromothiophen-3-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 470.0, found 470.2
87	2173		2-[(1 <i>R</i> ,2 <i>R</i>)-2-amino-3,3-difluorocyclohexyl]amino}- <i>N</i> -(4-chlorothiophen-3-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide acetate	Calc'd 426.1, found 426.4

88	6162		2-{[(1 <i>R</i> ,2 <i>R</i>)-2-amino-3,3-difluorocyclohexyl]amino}- <i>N</i> -(4-bromothiophen-3-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 470.0, found 470.2
89	342		2-{[(1 <i>R</i> ,2 <i>R</i>)-2-amino-3,3-difluorocyclohexyl]amino}- <i>N</i> -(4-cyanothiophen-3-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 417.1, found 417.4
90	1922		2-{[(1 <i>R</i> ,2 <i>R</i>)-2-amino-3,3-difluorocyclohexyl]amino}- <i>N</i> -(2-chlorothiophen-3-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 426.1, found 426.2
91	6371		<i>N</i> -(2-chlorothiophen-3-yl)-2-{[(1 <i>R</i> ,2 <i>S</i>)-2-hydroxycyclohexyl]amino}pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide	Calc'd 391.1, found 391.4

92	2060		2-{{(1R,2R)-2-amino-3,3-difluorocyclohexyl}amino}-N-(2-chlorophenyl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 420.1, found 420.2
93	6840		<i>N</i> -(2-chlorophenyl)-2-{{(1R,2S)-2-hydroxycyclohexyl}amino}pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 385.1, found 385.2
94	5626		2-{{(1R,2R)-2-amino-3,3-difluorocyclohexyl}amino}-N-(2-bromophenyl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 464.1, found 464.2
95	5864		<i>N</i> -(2-bromophenyl)-2-{{(1R,2S)-2-hydroxycyclohexyl}amino}pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 429.1, found 429.2
96	753		2-{{(1R,2R)-2-amino-3,3-difluorocyclohexyl}amino}-N-[4-(difluoromethyl)thiophe	Calc'd 442.1, found 442.4

			n-3-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	
97	1367		N-(2-cyanothiophen-3-yl)-2-{{(1 <i>R</i> ,2 <i>S</i>)-2-hydroxycyclohexyl}amino}pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 382.1, found 382.4
98	526		2-{{(1 <i>R</i> ,2 <i>R</i>)-2-amino-3,3-difluorocyclohexyl}amino}- <i>N</i> -(2-cyanothiophen-3-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 417.1, found 417.4

EXAMPLE 99



5

N-(1-Methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-(piperazin-1-yl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide (IRAK4 IC₅₀ = 63 nM)

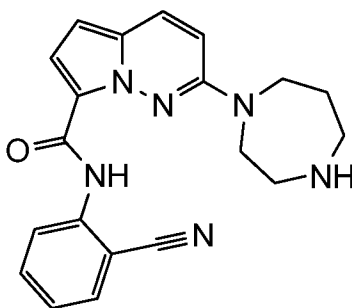
Step 1: Into a 25 mL sealed tube containing 2-hydroxy-*N*-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide (400 mg, 1.2 mmol) in tetrahydrofuran (4

10

mL), was added phosphorous oxychloride (2 mL, 18 mmol) followed by *N,N*-diisopropylethylamine (0.1 mL) and the reaction was heated at 100 °C for 16 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (silica gel) eluting with 20% ethyl acetate in petroleum ether to afford 2-chloro-*N*-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide as a solid and 2,5-dichloro-*N*-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide (60 mg, 9% yield) as an off white solid. For 2-Chloro-*N*-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide: MS [M+H]⁺ 344.5. For 2,5-Dichloro-*N*-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide: ¹H NMR (CDCl₃, 400 MHz): δ 10.79 (s, 1H), 8.39 (s, 1H), 7.95 (d, *J* = 9.6 Hz, 1H), 7.66 (s, 1H), 6.91 (d, *J* = 9.2 Hz, 1H), 3.98 (s, 3H). MS [M+H]⁺ 378.5.

Step 2: Into a 5 mL microwave vial containing 2-chloro-*N*-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide (25 mg, 0.07 mmol) in absolute ethanol (1 mL) were added *N,N*-diisopropylethylamine (0.03 mL, 0.14 mmol) and piperazine (8 mg, 0.09 mmol) and the reaction was irradiated under microwave at 150 °C for 20 h. The reaction mixture was concentrated under reduced pressure and purified by preparative HPLC to afford *N*-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-2-(piperazin-1-yl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide trifluoroacetate as a solid. ¹H NMR (CD₃OD, 400 MHz): δ 8.33 (s, 1H), 7.98 (d, *J* = 9.8 Hz, 1H), 7.47 (d, *J* = 4.8 Hz, 1H), 6.99 (d, *J* = 9.8 Hz, 1H), 6.62 (d, *J* = 4.8 Hz, 1H), 3.99 (s, 3H), 3.84 (t, *J* = 5.0 Hz, 4H), 3.44 (t, *J* = 5.0 Hz, 4H). MS calc'd [M+H]⁺ 394.2, found 394.0.

EXAMPLE 100



N-(2-Cyanophenyl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide (IRAK4 IC₅₀ = 866 nM)

Step 1: Into a 25 mL sealed tube containing a solution of 2-hydroxypyrrolo[1,2-*b*]pyridazine-7-carboxylic acid (500 mg, 2.8 mmol) in *N,N*-dimethylformamide (2 mL) were added 2-bromoaniline (580 mg, 3.4 mmol), *N,N*-diisopropylethylamine (2.0 mL, 9.8 mmol), 1-

[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (1.6 g, 4.2 mmol) and 1-hydroxybenzotriazole (76 mg, 0.06 mmol) and the reaction was heated at 60 °C for 16 h. The reaction mixture was brought to room temperature, concentrated under reduced pressure, diluted with ethyl acetate (15 mL) and water (15 mL) and stirred for 15 min.

5 The precipitate was filtered, washed with petroleum ether/diethyl ether and dried under reduced pressure to afford *N*-(2-bromophenyl)-2-hydroxypyrrolo[1,2-*b*]pyridazine-7-carboxamide as a solid. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 11.72 (s, 1H), 11.18 (s, 1H), 8.23 (d, *J* = 1.5 Hz, 1H), 8.21 (d, *J* = 1.5 Hz, 1H), 7.73-7.71 (m, 1H), 7.44-7.36 (m, 1H), 7.36 (d, *J* = 4.8 Hz, 1H), 7.14-7.10 (m, 1H), 6.67-6.64 (m, 2H). MS calc'd [M+H]⁺ 332.0, found 332.2.

10 Step 2: Into a 5 mL microwave vial containing a solution of *N*-(2-bromophenyl)-2-hydroxypyrrolo[1,2-*b*]pyridazine-7-carboxamide (70 mg, 0.12 mmol) in *N,N*-dimethylformamide (2 mL) were added *N,N*-diisopropylethylamine (0.13 mL, 0.74 mmol) and *N*-phenyl-bis(trifluoromethanesulfonimide) (83 mg, 0.23 mmol) and the reaction was stirred at room temperature for 1 h. To this mixture was added *tert*-butyl 1,4-diazepane-1-carboxylate (50
15 mg, 0.25 mmol) in *N,N*-dimethylformamide (0.3 mL) and the reaction was heated at 110 °C for 2 h. The reaction mixture was concentrated under reduced pressure, treated with aqueous ammonium chloride (3 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organics were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The solution was filtered, concentrated under reduced pressure and purified by flash chromatography (silica gel)
20 eluting with 35-40% ethyl acetate in petroleum ether to afford *tert*-butyl 4-(7-((2-bromophenyl)carbamoyl)pyrrolo[1,2-*b*]pyridazin-2-yl)-1,4-diazepane-1-carboxylate as a solid. MS calc'd [M+H]⁺ 514.1, found 514.4.

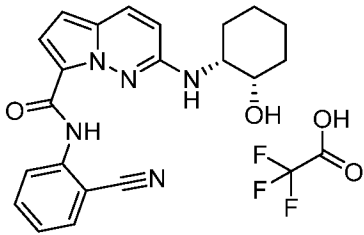
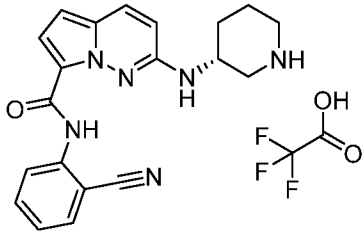
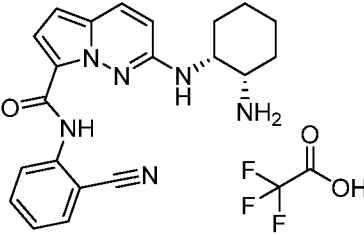
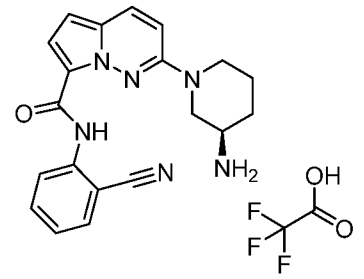
Step 3: In a 5 mL microwave vial containing a solution of *tert*-butyl 4-(7-((2-bromophenyl)carbamoyl)pyrrolo[1,2-*b*]pyridazin-2-yl)-1,4-diazepane-1-carboxylate (35 mg,
25 0.07 mmol) in *N,N*-dimethylformamide (2 mL) were added tetramethylethylenediamine (20 µL, 0.014 mmol) and zinc cyanide (7 mg, 0.06 mmol) and the reaction mixture was degassed under nitrogen atmosphere for 10 min. To this mixture were added 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (3 mg, 0.004 mmol) and tris(dibenzylideneacetone)dipalladium(0) (2 mg, 0.002 mmol) and the reaction mixture was irradiated under microwave at 120 °C for 20 min.
30 The reaction mixture was cooled to room temperature and filtered through celite pad and the filtrate was concentrated under reduced pressure and purified by flash chromatography (silica gel) eluting with 70-90% ethyl acetate in petroleum ether to afford *tert*-butyl 4-(7-((2-cyanophenyl)carbamoyl)pyrrolo[1,2-*b*]pyridazin-2-yl)-1,4-diazepane-1-carboxylate as a gum. MS calc'd [M+H]⁺ 461.2, found 461.2.

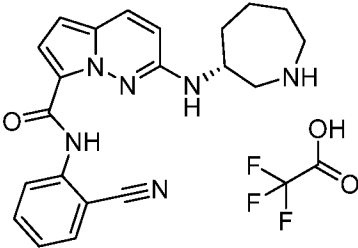
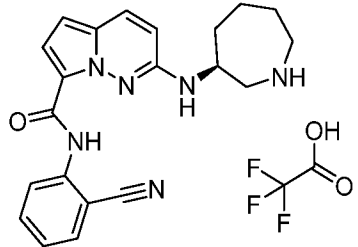
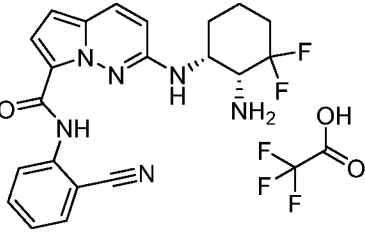
35 Step 4: Into a 10 mL round bottom flask containing *tert*-butyl 4-(7-((2-cyanophenyl)carbamoyl)pyrrolo[1,2-*b*]pyridazin-2-yl)-1,4-diazepane-1-carboxylate (25 mg) in dichloromethane (0.5 mL) was added trifluoroacetic acid (0.5 mL) and the reaction mixture was

stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and purified by preparative HPLC to afford *N*-(2-cyanophenyl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide trifluoroacetate as a solid. ¹H NMR (CD₃OD, 400 MHz): δ 8.01 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 9.9 Hz, 1H), 7.82 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.75 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.46 (d, *J* = 4.8 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 6.93 (d, *J* = 9.9 Hz, 1H), 6.61 (d, *J* = 4.8 Hz, 1H), 4.11 (t, *J* = 5.2 Hz, 2H), 3.94 (t, *J* = 6.0 Hz, 2H), 3.52 (t, *J* = 5.4 Hz, 2H), 3.37 (t, *J* = 5.7 Hz, 2H), 2.27-2.21 (m, 2H). MS calc'd [M+H]⁺ 361.2, found 361.4.

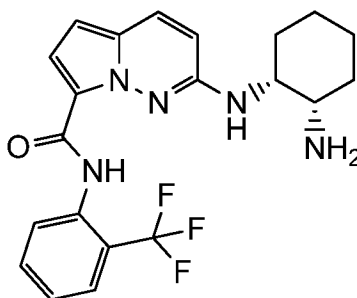
The following examples were prepared in an analogous manner of that described in Example 100.

<u>Example #</u>	<u>IRAK4</u> <u>IC₅₀ (nM)</u>	<u>Structure</u>	<u>IUPAC Name</u>	<u>Exact Mass</u> <u>[M+H]⁺</u>
101	574		<i>N</i> -(2-cyanophenyl)-2-piperazin-1-ylpyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 347.2, found 347.4
102	461		<i>N</i> -(2-cyanophenyl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 373.2, found 373.4
103	766		<i>N</i> -(2-cyanophenyl)-2-(5,8-diazaspiro[2.6]non-5-yl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 387.2, found 387.4

104	1861		<i>N</i> -(2-cyanophenyl)-2-([(1 <i>R</i> ,2 <i>S</i>)-2-hydroxycyclohexyl]amino)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 376.2, found 376.6
105	6		<i>N</i> -(2-cyanophenyl)-2-[(3 <i>R</i>)-piperidin-3-ylamino]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 361.2, found 361.4
106	6		2-([(1 <i>R</i> ,2 <i>S</i>)-2-aminocyclohexyl]amino)- <i>N</i> -(2-cyanophenyl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 375.2, found 375.4
107	26		2-[(3 <i>R</i>)-3-aminopiperidin-1-yl]- <i>N</i> -(2-cyanophenyl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 361.2, found 361.2

108	89		2-[(3 <i>R</i>)- or (3 <i>S</i>)-azepan-3-ylamino]- <i>N</i> -(2-cyanophenyl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 375.2, found 375.4
109	7		2-[(3 <i>R</i>)- or (3 <i>S</i>)-azepan-3-ylamino]- <i>N</i> -(2-cyanophenyl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 375.2, found 375.4
110	825		2-[(1 <i>R</i> ,2 <i>R</i>)-2-amino-3,3-difluorocyclohexyl]amino}- <i>N</i> -(2-cyanophenyl)pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 411.2, found 411.4

EXAMPLE 111



2-(1,4-Diazepan-1-yl)-*N*-(2-(trifluoromethyl)phenyl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide (IRAK4 IC₅₀ = 1424 nM)

Step 1: Into a 25 mL round bottom flask containing a solution of 2-hydroxypyrrolo[1,2-

- 5 *b*]pyridazine-7-carboxylic acid (150 mg, 1.4 mmol) in dichloromethane (5 mL) at 0 °C were added *N,N*-dimethylformamide (1 drop) and oxalyl chloride (0.3 mL, 2.8 mmol) dropwise. The mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was concentrated under nitrogen atmosphere to afford 2-hydroxypyrrolo[1,2-*b*]pyridazine-7-carbonyl chloride, which was taken to the next step without further purification.
- 10 Into a 10 mL round bottom flask charged with 2-(trifluoromethyl)aniline (0.34 g, 2.2 mmol) and *N,N*-diisopropylethylamine (0.5 mL, 2.8 mmol) in dichloromethane (5 mL) at 0 °C was added 2-hydroxypyrrolo[1,2-*b*]pyridazine-7-carbonyl chloride in dichloromethane (2 mL) dropwise. The reaction mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was treated with ice cold water (2 mL) and extracted with dichloromethane (2 x 5 mL). The
- 15 combined organic layers were washed with brine (10 mL) and dried over anhydrous sodium sulfate. The solution was filtered, concentrated under reduced pressure and purified by flash chromatography (silica gel) eluting with 30-35% ethyl acetate in petroleum ether to afford 2-hydroxy-*N*-(2-(trifluoromethyl)phenyl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide as a solid. ¹H NMR (CD₃OD, 400 MHz): δ 7.99 (d, *J* = 9.5 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 7.8
- 20 Hz, 1H), 7.73-7.69 (m, 1H), 7.48-7.45 (m, 2H), 6.65-6.61 (m, 2H). MS calc'd [M+H]⁺ 322.1, found 322.4.

Step 2: Into a 5 mL microwave vial containing a solution of 2-hydroxy-*N*-(2-

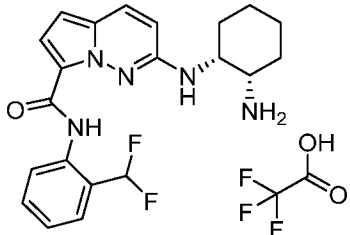
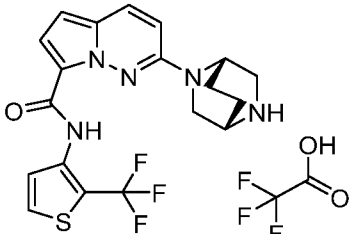
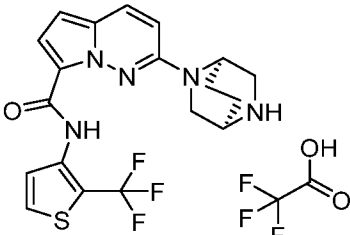
- (trifluoromethyl)phenyl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide (25 mg, 0.08 mmol) in *N,N*-dimethylformamide (2 mL) were added *N,N*-diisopropylethylamine (0.05 mL, 0.27 mmol) and
- 25 *N*-phenyl-bis(trifluoromethanesulfonimide) (31 mg, 0.09 mmol) and the reaction mixture was stirred at room temperature for 1 h. To this was added *tert*-butyl 1,4-diazepane-1-carboxylate (19 mg, 0.09 mmol) in *N,N*-dimethylformamide (0.3 mL) and the reaction was heated at 110 °C for 2 h. The reaction mixture was treated with ice cold water (5 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine (5 mL) and dried
- 30 over anhydrous sodium sulfate. The solution was filtered, concentrated under reduced pressure and purified by flash chromatography (silica gel) using 35-40% ethyl acetate in petroleum ether to afford *tert*-butyl 4-(7-((2-(trifluoromethyl)phenyl)carbamoyl)pyrrolo[1,2-*b*]pyridazin-2-yl)-1,4-diazepane-1-carboxylate as a solid. MS calc'd [M+H]⁺ 518.2, found 518.6.

Step 3: Into a 10 mL round bottom flask charged with *tert*-butyl 4-(7-((2-

- 35 (trifluoromethyl)phenyl)carbamoyl)pyrrolo[1,2-*b*]pyridazin-2-yl)-1,4-diazepane-1-carboxylate (25 mg) in dichloromethane (2 mL) was added trifluoroacetic acid (0.5 mL) and the reaction was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced

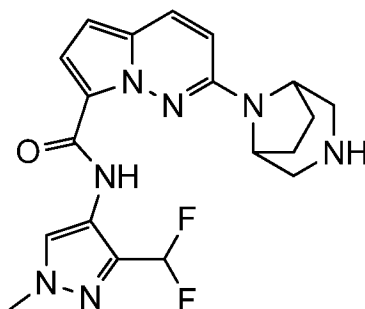
pressure and purified by preparative HPLC to afford 2-(1,4-diazepan-1-yl)-N-(2-(trifluoromethyl)phenyl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide trifluoroacetate as a solid. ¹H NMR (CD₃OD, 400 MHz): δ 7.96 (d, *J* = 9.9 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.75-7.71 (m, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.42 (d, *J* = 4.8 Hz, 1H), 6.91 (d, *J* = 9.9 Hz, 1H), 6.61 (d, *J* = 4.8 Hz, 1H), 4.00 (t, *J* = 5.2 Hz, 2H), 3.83 (t, *J* = 6.0 Hz, 2H), 3.44 (t, *J* = 5.4 Hz, 2H), 3.33 (t, *J* = 5.4 Hz, 2H), 2.21-2.16 (m, 2H). MS calc'd [M+H]⁺ 404.2, found 404.4.

The following examples were prepared in an analogous manner of that described in Example 111.

<u>Example #</u>	<u>IRAK4 IC₅₀ (nM)</u>	<u>Structure</u>	<u>IUPAC Name</u>	<u>Exact Mass [M+H]⁺</u>
112	472		2-([(1 <i>R</i> ,2 <i>S</i>)-2-aminocyclohexyl]amino)- <i>N</i> -[2-(difluoromethyl)phenyl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 400.2, found 400.4
113	1215		2-[(1 <i>S</i> ,4 <i>S</i>)- or (1 <i>R</i> ,4 <i>R</i>)-2,5-diazabicyclo[2.2.2]oct-2-yl]- <i>N</i> -[2-(trifluoromethyl)thiophen-3-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 422.2, found 422.4
114	1771		2-[(1 <i>S</i> ,4 <i>S</i>)- or (1 <i>R</i> ,4 <i>R</i>)-2,5-diazabicyclo[2.2.2]oct-2-yl]- <i>N</i> -[2-(trifluoromethyl)thiophen-3-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 422.2, found 422.4

			carboxamide trifluoroacetate	
115	2015		2-(1,4-diazepan-1-yl)- N-[2- (trifluoromethyl)thiop hen-3-yl]pyrrolo[1,2- b]pyridazine-7- carboxamide trifluoroacetate	Calc'd 410.1, found 410.4
116	221		2-{[(1R,2S)-2- aminocyclohexyl]amin o}-N-[2- (trifluoromethyl)thiop hen-3-yl]pyrrolo[1,2- b]pyridazine-7- carboxamide trifluoroacetate	Calc'd 424.1, found 424.4
117	2985		2-{[(1R,2R)-2-amino- 3,3- difluorocyclohexyl]am ino}-N-[2- (trifluoromethyl)thiop hen-3-yl]pyrrolo[1,2- b]pyridazine-7- carboxamide trifluoroacetate	Calc'd 460.0, found 460.4
118	7391		2-{[(1R,2R)-2-amino- 3,3- difluorocyclohexyl]am ino}-N-[2- (difluoromethyl)pheny l]pyrrolo[1,2- b]pyridazine-7- carboxamide trifluoroacetate	Calc'd 436.1, found 436.4

EXAMPLE 119



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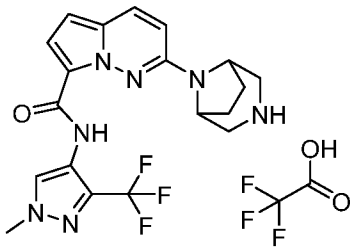
2-(3,8-Diazabicyclo[3.2.1]octan-8-yl)-*N*-(3-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide (IRAK4 IC₅₀ = 0.5 nM)

- Step 1: Into a 10 mL round bottom flask containing a solution of *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.33 mmol) in dichloromethane (2 mL) at 0 °C were added triethylamine (0.14 mL, 0.99 mmol) and trifluoroacetic anhydride (0.1 mL, 0.49 mmol) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was treated with water (3 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure and purified by flash chromatography (silica gel) eluting with 20-30% ethyl acetate in petroleum ether to afford *tert*-butyl 3-(2,2,2-trifluoroacetyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate as a liquid. MS calc'd [M-Boc+H]⁺ 209.1, found 209.4.
- Step 2: Into a 10 mL round bottom flask containing a solution of *tert*-butyl 3-(2,2,2-trifluoroacetyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80 mg, 0.26 mmol) in dichloromethane (2 mL) at 0 °C was added trifluoroacetic acid (0.2 mL) and the reaction was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to afford 1-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2,2,2-trifluoroethan-1-one trifluoroacetate, which was directly taken to the next step. MS calc'd [M+H]⁺ 209.1, found 209.4.
- Step 3: Into a 5 mL microwave vial containing a solution of 2-hydroxy-*N*-(2-(trifluoromethyl)phenyl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide (35 mg, 0.11 mmol) in *N,N*-dimethylformamide (2 mL) were added *N,N*-diisopropylethylamine (0.1 mL, 0.34 mmol) and *N*-phenyl-bis(trifluoromethanesulfonyl)imide (44 mg, 0.13 mmol) and the reaction was stirred at room temperature for 1 h. To this mixture was added 1-(3,8-diazabicyclo[3.2.1]octan-3-yl)-2,2,2-trifluoroethan-1-one trifluoroacetate (60 mg, 0.22 mmol) in *N,N*-dimethylformamide (0.3 mL) and the reaction was heated at 110 °C for 2 h. The reaction mixture was treated with ice

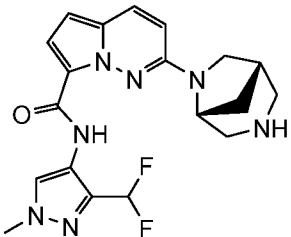
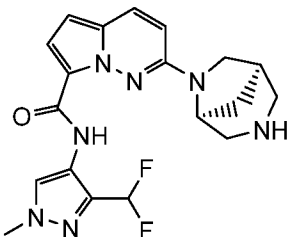
cold water (2 mL) and extracted with ethyl acetate (2 x 5 mL). The combined organics were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The solution was filtered, concentrated under reduced pressure and purified by flash chromatography (silica gel) eluting with 30-35% ethyl acetate in petroleum ether to afford *N*-(3-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-2-(3-(2,2,2-trifluoroacetyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide as a solid. MS calc'd $[M+H]^+$ 498.2, found 498.2.

Step 4: Into a 10 mL round bottom flask containing a solution of *N*-(3-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-2-(3-(2,2,2-trifluoroacetyl)-3,8-diazabicyclo[3.2.1]octan-8-yl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide (30 mg, 0.06 mmol) in methanol (5 mL) and water (1 mL) was added potassium carbonate (25 mg, 0.18 mmol) and the reaction was stirred at room temperature for 16 h. The reaction mixture was concentrated, cooled to 0 °C and acidified to pH 4 using 1.5 N HCl. The reaction mixture was extracted with ethyl acetate (2 x 5 mL). The combined organics were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure and purified by preparative HPLC to afford 2-(3,8-diazabicyclo[3.2.1]octan-8-yl)-*N*-(3-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)pyrrolo[1,2-*b*]pyridazine-7-carboxamide trifluoroacetate as a solid. ^1H NMR (CD_3OD , 400 MHz): δ 8.32 (s, 1H), 7.97 (d, $J = 9.6$ Hz, 1H), 7.46 (d, $J = 4.8$ Hz, 1H), 6.92 (d, $J = 54.0$ Hz, 1H), 6.88 (d, $J = 9.6$ Hz, 1H), 6.61 (d, $J = 4.4$ Hz, 1H), 3.94 (s, 3H), 3.46-3.43 (m, 2H), 3.33-3.30 (m, 2H), 3.28-3.25 (m, 2H), 2.37-2.34 (m, 2H), 2.15-2.09 (m, 2H). MS calc'd $[M+H]^+$ 402.2, found 402.4.

The following examples were prepared in an analogous manner of that described in Example 119.

<u>Example #</u>	<u>IRAK4 IC₅₀ (nM)</u>	<u>Structure</u>	<u>IUPAC Name</u>	<u>Exact Mass [M+H]⁺</u>
120	2		2-(3,8-diazabicyclo[3.2.1]oct-8-yl)- <i>N</i> -[1-methyl-3-(trifluoromethyl)-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide trifluoroacetate	Calc'd 420.2, found 420.4

121	ND		2-(3,6-diazabicyclo[3.2.1]oct-6-yl)- <i>N</i> -[1-methyl-3-(trifluoromethyl)-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide	Calc'd 420.2, found 420.4
122	39		2-[(1 <i>S</i> ,5 <i>R</i>)-3,6-diazabicyclo[3.2.1]oct-6-yl]- <i>N</i> -[1-methyl-3-(trifluoromethyl)-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide	Calc'd 420.2, found 420.4
123	114		2-[(1 <i>S</i> ,5 <i>R</i>)-3,6-diazabicyclo[3.2.1]oct-6-yl]- <i>N</i> -[1-methyl-3-(trifluoromethyl)-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide	Calc'd 420.2, found 420.4
124	ND		2-(3,6-diazabicyclo[3.2.1]oct-6-yl)- <i>N</i> -[3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide	Calc'd 402.2, found 402.4

125	5		2-[(1 <i>S</i> ,5 <i>R</i>)- or (1 <i>R</i> ,5 <i>S</i>)-3,6-diazabicyclo[3.2.1]oct-6-yl]- <i>N</i> -[3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide	Calc'd 402.2, found 402.4
126	14		2-[(1 <i>S</i> ,5 <i>R</i>)- or (1 <i>R</i> ,5 <i>S</i>)-3,6-diazabicyclo[3.2.1]oct-6-yl]- <i>N</i> -[3-(difluoromethyl)-1-methyl-1 <i>H</i> -pyrazol-4-yl]pyrrolo[1,2- <i>b</i>]pyridazine-7-carboxamide	Calc'd 402.2, found 402.4

BIOLOGICAL DATA

Compounds of the instant invention were tested by the assay described below and were found to have IRAK4 inhibitory activity. Data is shown for all compounds in the representative table(s) and Examples. Other assays are known in the literature and could be readily performed by those of skill in the art.

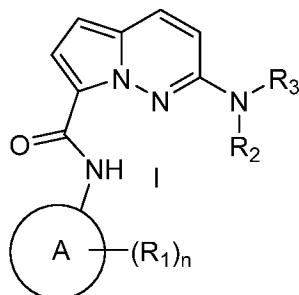
IRAK4 kinase assay

The kinase activity of IRAK4 is determined by its ability to catalyze the phosphorylation of a fluorescent polypeptide substrate. The extent of phosphorylation is measured using the IMAP technology (Molecular Devices) where the phosphorylated fluorescent substrate binds to the large M(III)-based nanoparticles which reduces the rotational speed of the substrate and thus increases its fluorescent polarization (FP).

20 μ L reaction mixture contains 10 mM TrisHCl, pH 7.2, 0.5 nM GST tagged IRAK4 (SignalChem), 100 nM fluorescent peptide substrate (RP7030, Molecular Devices), 100 μ M ATP, 1 mM DDT, 1 mM MgCl₂, and 0.01% Tween 20. The reaction is initiated by the addition of ATP. After incubation for 30 minutes at 25 °C, 60 μ L of Progressive IMAP Reagent (Molecular Devices) is added to stop the reaction. Change in RP7030's FP is determined by a FP reader (Analyst HT, LJJL BioSystems).

WHAT IS CLAIMED IS:

1. A compound according to Formula I:



5 wherein:

Ring A is aryl or heterocyclyl;

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

10 R_1 is independently selected from: (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, heterocyclyl, CF₃, CHF₂, CN, halo, said alkyl, cycloalkyl and heterocyclyl optionally substituted with halo, OH, CH₃, and OCH₃;

15 R_2 is H and R_3 is independently selected from: (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, and heterocyclyl each optionally substituted with one or more halo, OH, N(R_b)₂, or morpholinyl, or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form a heterocyclyl, said heterocyclyl optionally substituted with one or more substituents selected from R_a ;

R_a is independently selected from (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, CF₃, CHF₂, OH, halo and NH₂, said alkyl optionally substituted with (C₃-C₆)cycloalkyl and CF₃; and

R_b is independently selected from H and (C₁-C₄)alkyl;
or a pharmaceutically acceptable salt thereof.

20

2. A compound according to Claim 1 of Formula I:

wherein:

Ring A is pyrazolyl, pyridinyl, thiophenyl, furanyl or phenyl;

n is 0, 1 or 2;

25 R_1 is independently selected from: (C₁-C₄)alkyl, cyclopropyl, oxadiazolyl, pyridinyl, oxazolyl, triazolyl, pyrimidinyl, CF₃, CHF₂, CN and halo, said alkyl, oxadiazolyl, pyridinyl, oxazolyl, triazolyl and pyrimidinyl are optionally substituted with halo, OH, CH₃, and OCH₃;

30 R_2 is H and R_3 is independently selected from: (C₁-C₄)alkyl, cyclohexyl, cycloheptyl, piperidinyl and azepanyl each optionally substituted with one or more F, OH,

N(R_b)₂, or morpholinyl, or R₂ and R₃ can be taken together with the nitrogen to which they are attached to form a heterocyclyl selected from piperazinyl, diazepanyl, diazabicyclooctyl, diazabicycloheptyl, diazaspirononyl, hexahydropyrrolopyrazinyl, piperidinyl, diazabicyclononyl, oxadiazabicyclodecyl and diazatricyclodecyl, said heterocyclyl optionally substituted with one or more substituents selected from R_a;

R_a is independently selected from (C₁-C₄)alkyl, cyclopropyl, CF₃, CHF₂, OH, F and NH₂, said alkyl optionally substituted with cyclopropyl and CF₃; and

R_b is independently selected from H and methyl;
or a pharmaceutically acceptable salt thereof.

3. A compound which is selected from:

2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-(3,6-diazabicyclo[3.2.1]oct-3-yl)-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-[(1S,5S)-3,6-diazabicyclo[3.2.1]oct-3-yl]-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-[(1R,5R)-3,6-diazabicyclo[3.2.1]oct-3-yl]-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-{[(1R,2S)-2-hydroxycyclohexyl]amino}-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]-2-[(3R)-piperidin-3-ylamino]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-{[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-(2,5-diazabicyclo[2.2.2]oct-2-yl)-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-(5,8-diazaspiro[2.6]non-5-yl)-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-(1,4-diazepan-1-yl)-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-(2,5-diazabicyclo[2.2.2]oct-2-yl)-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-[(3R)-3-aminopiperidin-1-yl]-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

- 2-[(3R)-3-aminopiperidin-1-yl]-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]-2-piperazin-1-ylpyrrolo[1,2-b]pyridazine-7-carboxamide;
- 5 2-(1,4-diazepan-1-yl)-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]-2-[(3R)-piperidin-3-ylamino]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 10 2-(2,5-diazabicyclo[2.2.2]oct-2-yl)-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-(5,8-diazaspiro[2.6]non-5-yl)-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 15 2-[(1R,2S)-2-aminocyclohexyl]amino}-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]-2-[(1R,2S)-2-hydroxycyclohexyl]amino}pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 20 N-(3-bromo-1-methyl-1H-pyrazol-4-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-[(1R,2S)-2-aminocyclohexyl]amino}-N-(3-bromo-1-methyl-1H-pyrazol-4-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 25 N-(3-chloro-1-methyl-1H-pyrazol-4-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-(azepan-3-ylamino)-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 30 2-[(1R,2S)-2-aminocyclohexyl]amino}-N-(3-chloro-1-methyl-1H-pyrazol-4-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(3-chloro-1-methyl-1H-pyrazol-4-yl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 35 N-(3-bromo-1-methyl-1H-pyrazol-4-yl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-[(1R,2S)-2-aminocyclohexyl]amino}-N-(3-cyano-1-methyl-1H-pyrazol-4-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 35 N-(3-cyano-1-methyl-1H-pyrazol-4-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;

- N-(3-cyano-1-methyl-1H-pyrazol-4-yl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-{[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(3-bromo-1-methyl-1H-pyrazol-4-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 5 N-(3-chloro-1-methyl-1H-pyrazol-4-yl)-2-[(1S,4S)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(3-chloro-1-methyl-1H-pyrazol-4-yl)-2-[(1R,4R)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(3-bromo-1-methyl-1H-pyrazol-4-yl)-2-[(1S,4S)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 10 N-(3-bromo-1-methyl-1H-pyrazol-4-yl)-2-[(1R,4R)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide
2-[(1S,4S)-2,5-diazabicyclo[2.2.2]oct-2-yl]-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 15 2-[(1R,4R)-2,5-diazabicyclo[2.2.2]oct-2-yl]-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-[(3R)-azepan-3-ylamino]-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-[(3S)-azepan-3-ylamino]-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 20 2-[(3R)-azepan-3-ylamino]-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-[(3S)-azepan-3-ylamino]-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 25 N-(3-cyano-1-methyl-1H-pyrazol-4-yl)-2-[(1S,4S)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(3-cyano-1-methyl-1H-pyrazol-4-yl)-2-[(1R,4R)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-[1-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 30 2-(3,8-diazabicyclo[3.2.1]oct-3-yl)-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-(3,8-diazabicyclo[3.2.1]oct-3-yl)-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 35 2-{[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(3-chloro-1-methyl-1H-pyrazol-4-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;

- 2-(3,6-diazabicyclo[3.2.1]oct-3-yl)-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-[(1S,5S)-3,6-diazabicyclo[3.2.1]oct-3-yl]-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
5 2-[(1R,5R)-3,6-diazabicyclo[3.2.1]oct-3-yl]-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(3-cyano-1-methyl-1H-pyrazol-4-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(3-chloro-1-methyl-1H-pyrazol-4-yl)-2-[(1R,2S)-2-hydroxycyclohexyl]amino}pyrrolo[1,2-b]pyridazine-7-carboxamide;
10 N-[1-tert-butyl-3-(difluoromethyl)-1H-pyrazol-4-yl]-2-[(1R,2S)-2-hydroxycyclohexyl]amino}pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-[3-(difluoromethyl)-1-(1-methylethyl)-1H-pyrazol-4-yl]-2-[(1R,2S)-2-hydroxycyclohexyl]amino}pyrrolo[1,2-b]pyridazine-7-carboxamide;
15 2-(2,5-diazabicyclo[2.2.2]oct-2-yl)-N-[4-(difluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-bromophenyl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-[(1R,2S)-2-aminocyclohexyl]amino}-N-(2-bromophenyl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
20 N-(2-chlorophenyl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(4-bromothiophen-3-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-bromophenyl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(4-bromothiophen-3-yl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
25 2-[(1R,2S)-2-aminocyclohexyl]amino}-N-(4-bromothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-chlorophenyl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-[(1R,2S)-2-aminocyclohexyl]amino}-N-(2-chlorophenyl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
30 N-(2-chlorothiophen-3-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-cyanothiophen-3-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(4-cyanothiophen-3-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-(1,4-diazepan-1-yl)-N-[4-(difluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
35 N-(2-chlorothiophen-3-yl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;

- 2-{{(1R,2S)-2-aminocyclohexyl}amino}-N-(2-chlorothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-{{(1R,2S)-2-aminocyclohexyl}amino}-N-[4-(difluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 5 2-{{(1R,2S)-2-aminocyclohexyl}amino}-N-(4-cyanothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- N-(4-cyanothiophen-3-yl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-{{(1R,2S)-2-aminocyclohexyl}amino}-N-(2-cyanothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-
- 10 carboxamide;
- N-(2-bromothiophen-3-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-{{(1R,2S)-2-aminocyclohexyl}amino}-N-(2-bromothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- N-(2-bromothiophen-3-yl)-2-[(1S,4S)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-
- 15 7-carboxamide;
- N-(2-bromothiophen-3-yl)-2-[(1R,4R)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- N-(2-cyanothiophen-3-yl)-2-[(1S,4S)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 20 N-(2-cyanothiophen-3-yl)-2-[(1R,4R)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- N-(4-chlorothiophen-3-yl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- N-(4-chlorothiophen-3-yl)-2-[(1S,4S)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 25 N-(4-chlorothiophen-3-yl)-2-[(1R,4R)-2,5-diazabicyclo[2.2.2]oct-2-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-{{(1R,2S)-2-aminocyclohexyl}amino}-N-(4-chlorothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-{{(1R,2R)-2-amino-3,3-difluorocyclohexyl}amino}-N-(2-bromothiophen-3-yl)pyrrolo[1,2-
- 30 b]pyridazine-7-carboxamide;
- 2-{{(1R,2R)-2-amino-3,3-difluorocyclohexyl}amino}-N-(4-chlorothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-{{(1R,2R)-2-amino-3,3-difluorocyclohexyl}amino}-N-(4-bromothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 35 2-{{(1R,2R)-2-amino-3,3-difluorocyclohexyl}amino}-N-(4-cyanothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;

- 2-{[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(2-chlorothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-chlorothiophen-3-yl)-2-{[(1R,2S)-2-hydroxycyclohexyl]amino}pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 5 2-{[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(2-chlorophenyl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-chlorophenyl)-2-{[(1R,2S)-2-hydroxycyclohexyl]amino}pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 10 2-{[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(2-bromophenyl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-bromophenyl)-2-{[(1R,2S)-2-hydroxycyclohexyl]amino}pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 15 2-{[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-[4-(difluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-cyanothiophen-3-yl)-2-{[(1R,2S)-2-hydroxycyclohexyl]amino}pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 20 2-{[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(2-cyanothiophen-3-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]-2-piperazin-1-ylpyrrolo[1,2-b]pyridazine-7-carboxamide;
- 25 N-(2-cyanophenyl)-2-(1,4-diazepan-1-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-cyanophenyl)-2-piperazin-1-ylpyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-cyanophenyl)-2-(2,5-diazabicyclo[2.2.2]oct-2-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-cyanophenyl)-2-(5,8-diazaspiro[2.6]non-5-yl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 30 N-(2-cyanophenyl)-2-{[(1R,2S)-2-hydroxycyclohexyl]amino}pyrrolo[1,2-b]pyridazine-7-carboxamide;
N-(2-cyanophenyl)-2-[(3R)-piperidin-3-ylamino]pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-(2-cyanophenyl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 35 2-[(3R)-3-aminopiperidin-1-yl]-N-(2-cyanophenyl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-[(3R)-azepan-3-ylamino]-N-(2-cyanophenyl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-[(3S)-azepan-3-ylamino]-N-(2-cyanophenyl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
2-{[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-(2-cyanophenyl)pyrrolo[1,2-b]pyridazine-7-carboxamide;
- 2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-[2-(trifluoromethyl)phenyl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-[2-(difluoromethyl)phenyl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-[(1S,4S)-2,5-diazabicyclo[2.2.2]oct-2-yl]-N-[2-(trifluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

5 2-[(1R,4R)-2,5-diazabicyclo[2.2.2]oct-2-yl]-N-[2-(trifluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-(1,4-diazepan-1-yl)-N-[2-(trifluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

10 2-{[(1R,2S)-2-aminocyclohexyl]amino}-N-[2-(trifluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-{[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-[2-(trifluoromethyl)thiophen-3-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-{[(1R,2R)-2-amino-3,3-difluorocyclohexyl]amino}-N-[2-(difluoromethyl)phenyl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

15 2-(3,8-diazabicyclo[3.2.1]oct-8-yl)-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-(3,8-diazabicyclo[3.2.1]oct-8-yl)-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

20 2-(3,6-diazabicyclo[3.2.1]oct-6-yl)-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-[(1S,5R)-3,6-diazabicyclo[3.2.1]oct-6-yl]-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-[(1R,5S)-3,6-diazabicyclo[3.2.1]oct-6-yl]-N-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

25 2-(3,6-diazabicyclo[3.2.1]oct-6-yl)-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

2-[(1S,5R)-3,6-diazabicyclo[3.2.1]oct-6-yl]-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide; and

30 2-[(1R,5S)-3,6-diazabicyclo[3.2.1]oct-6-yl]-N-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]pyrrolo[1,2-b]pyridazine-7-carboxamide;

or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition comprising a pharmaceutical
35 carrier and a therapeutically effective amount of a compound of Claim 1.

5. The use of the compound according to Claim 1 for the preparation of a medicament useful in the treatment or prevention of an inflammation related disease in a mammal in need of such treatment.

5 6. A compound of Claim 1 for use in therapy.

7. A method for treating an inflammatory disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Claim 1 or a pharmaceutically acceptable salt thereof.

10

8. The method according to Claim 7 wherein the inflammatory disease is selected from rheumatoid arthritis, inflammatory bowel disease and cancer.

9. A method of treating an inflammatory disease which comprises administering a therapeutically effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, in combination with a second therapeutic agent.

15

10. The method of Claim 9 wherein the second therapeutic agent is selected from an anti-cancer agent and an anti-inflammatory agent.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/21121

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/5025; C07D 487/04 (2016.01)

CPC - A61K 31/5025; C07D 487/04

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(8): A61K 31/5025; A61P 29/00, 35/00; C07D 487/04 (2016.01)

CPC: A61K 31/5025; C07D 487/04 USPC: 514/248; 544/235

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)

PATSEER (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, Other Countries (INPADOC), RU, AT, CH, TH, BR, PH); EBSCO; Google Scholar; IP.com; SureChEMBL; KEYWORDS: pyrazolo pyrimidin*, pyrazolo 1 5 a pyrimidin*, IRAK* modulat*, IRAK* 4, treat* inflammat*, rheumatoid arthritis, inflammatory bowel disease*, treat* cancer*, inhibit* IRAK 4, pyrrolo pyridazine, pyrrolo 1 2 b pyridazine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2014/0303149 A1 (HOFFMANN-LA ROCHE INC.) 09 October 2014; paragraphs [0006], [0085], [0122], [0132], [0134]-[0136], [0138], [0149], [0155]-[0156], [0169], [0462], [0464], [0466], [0478], [0481]-[0482]	1-10
Y	US 2004/0209886 A1 (SALVATI, ME et al.) 21 October 2004; paragraphs [0018]-[0021], [0023], [0025]-[0026], [0028]-[0032], [0038], [0040], [0140]-[0141], [0151]	1-10
A	WO 2009/095253 A1 (MERZ PHARMA GMBH & CO. KGAA) 06 August 2009; entire document	1-10

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

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"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

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26 April 2016 (26.04.2016)

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