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(54) Title:

**AMINO-HETEROCYCLIC COMPOUNDS USED AS PDE9  
INHIBITORS**

(57) **Abstract:**

The invention provides PDE9-inhibiting compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein R1, R2, R3, A1 and n are as defined herein. Pharmaceutical compositions containing the compounds of Formula I, and uses thereof in treating neurodegenerative and cognitive disorders, such as Alzheimer's disease and schizophrenia, are also provided.



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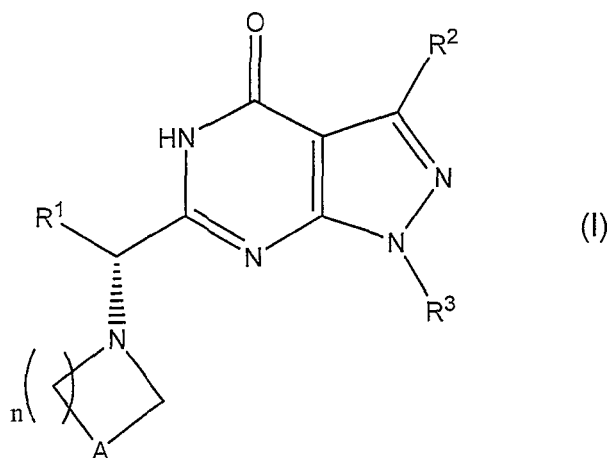
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## (54) Title: AMINO-HETEROCYCLIC COMPOUNDS USED AS PDE9 INHIBITORS



(57) Abstract: The invention provides PDE9-inhibiting compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein  $R^1$ ,  $R^2$ ,  $R^3$ , A1 and n are as defined herein. Pharmaceutical compositions containing the compounds of Formula I, and uses thereof in treating neurodegenerative and cognitive disorders, such as Alzheimer's disease and schizophrenia, are also provided.

## AMINO-HETEROCYCLIC COMPOUNDS USED AS PDE9 INHIBITORS

FIELD OF THE INVENTION

This invention relates to a series of novel compounds that are selective inhibitors of phosphodiesterase type 9 ("PDE9"). More particularly, the invention relates to pyrazolo[3,4-d]pyrimidinone compounds for use in the treatment and prevention of neurodegenerative diseases and other diseases and disorders influenced by modulation of PDE9.

BACKGROUND OF THE INVENTION

Cyclic nucleotides cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) are important second messengers and thus are central to the control and regulation of a multitude of cellular events, both physiological and pathophysiological, in a wide variety of organs.

Cyclic GMP is formed from GTP by the catalytic reaction of guanylyl cyclase (GC), which is activated by nitric oxide (NO). Cyclic GMP in turn activates cGMP-dependent protein kinases (cGK), which mediate local and global signaling. A variety of physiological processes in the cardiovascular, nervous and immune systems are controlled by the NO/cGMP pathway, including ion channel conductance, glycogenolysis, cellular apoptosis, and smooth muscle relaxation. In blood vessels, relaxation of vascular smooth muscles leads to vasodilation and increased blood flow.

The phosphodiesterase (PDE) enzyme family hydrolyzes cGMP and cAMP. The PDE9 enzyme has been identified as a novel member of the PDE enzyme family that selectively hydrolyzes cGMP over cAMP. See Fisher *et al.*, *J. Biol. Chem.*, 273(25), 15559-15564 (1998). PDE9 has been found to be present in a variety of human tissues, namely the testes, brain, small intestine, skeletal muscle, heart, lung, thymus and spleen, as well as in smooth muscle cells within the human vasculature of a variety of tissues.

Recent studies have directly implicated dysfunction of NO/cGMP/cGK signaling in Alzheimer's disease. For example, disruption of Long Term Potentiation (LTP), a physiological correlate of learning and memory, by amyloid- $\beta$  peptide was shown to result from a malfunction of NO/cGMP

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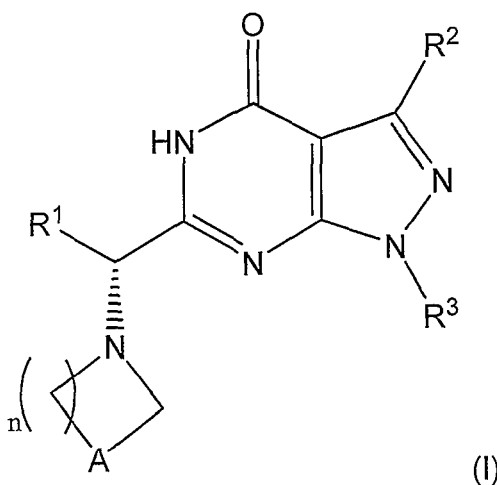
signaling. Puzzo *et al.*, *J. Neurosci.*, 25(29):6887-6897 (2005). Moreover, in rats showing deficits in memory tasks due to depletion in forebrain acetylcholinesterase (which is associated with Alzheimer's disease), administration of a nitric oxide mimetic increased GC activity and reversed the cognitive deficits in memory tasks. Bennett *et al.*, *Neuropsychopharmacology*, 32:505-513 (2007). It is therefore believed that therapeutic agents capable of enhancing the GC/NO/cGMP/cGK signaling cascade may be useful as a new approach to the treatment of Alzheimer's disease and other neurodegenerative disorders.

By reducing or preventing the hydrolysis of cGMP by PDE9, PDE9 inhibitors elevate the intracellular level of cGMP, thus enhancing or prolonging its effects. It has been found that an increase in cGMP concentration in rats leads to improvement in learning and memory in social and object recognition tests. See, e.g., Boess *et al.*, *Neuropharmacology*, 47:1081-1092 (2004). Inhibition of PDE9 has been shown to increase LTP. Hendrix, *BMC Pharmacol.*, 5(Supp 1):55 (2005).

Accordingly, there is a need for PDE9 inhibitors that are effective in treating conditions that may be regulated or normalized by inhibition of PDE9.

### SUMMARY OF THE INVENTION

The present invention is directed to compounds of Formula (I),



and pharmaceutically acceptable salts thereof, wherein  $R^1$ ,  $R^2$ ,  $R^3$ , A and n are as defined herein.

The present invention is also directed to pharmaceutical compositions containing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle, carrier or diluent, and optionally further comprising a second pharmaceutical agent.

The present invention is further directed to a method of inhibiting PDE9 in a mammal in need of such inhibition, comprising the step of administering to the mammal a PDE9-inhibiting amount of a) a compound of Formula I, or a pharmaceutically acceptable salt thereof; or b) a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle, carrier or diluent.

The present invention is further directed to a method of treating a neurodegenerative disease in a mammal in need of such treatment, comprising the step of administering to the mammal a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention is further directed to a method of promoting neurorestoration in a mammal in need of such neurorestoration, comprising the step of administering to the mammal a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention is still further directed to a method of promoting functional recovery in a mammal suffering from an injury of the brain, comprising the step of administering to the mammal a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

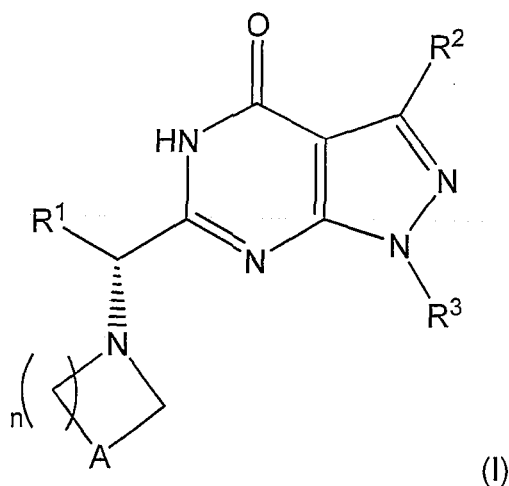
The present invention is still further directed to a method of improving cognitive deficits and treating cognitive impairment in a mammal in need of such improvement or treatment, comprising the step of administering to the mammal a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention is still further directed to a method of enhancing cognition in a mammal in need of such enhancement, comprising the step of administering to the mammal a cognition-enhancing amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

5 With the foregoing and other advantages and features of the invention that will become hereinafter apparent, the nature of the invention may be more clearly understood by reference to the following detailed description of the invention and the appended claims.

### **DETAILED DESCRIPTION OF THE INVENTION**

10 The present invention comprises novel selective PDE9 inhibitors of Formula (I),



and pharmaceutically acceptable salts thereof, wherein:

15 R<sup>1</sup> is selected from the group consisting of (i) hydrogen, (ii) (C<sub>1</sub>-C<sub>4</sub>)alkyl, (iii) (C<sub>2</sub>-C<sub>4</sub>)alkenyl, (iv) (C<sub>2</sub>-C<sub>4</sub>)alkynyl, (v) (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (vi) (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (vii) (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, optionally substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, cyano, carboxy, and carbamoyl, (viii) 4 to 10 member  
20 heterocycloalkyl, optionally substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, cyano, carboxy, and carbamoyl, (ix) aryl, optionally substituted with one to three

substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, cyano, carboxy, and carbamoyl, and (x) heteroaryl, optionally substituted with one to three substituents, the substituents being  
5 independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, cyano, carboxy, and carbamoyl;

R<sup>2</sup> is selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, cyano, and (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl;

10 R<sup>3</sup> is selected from the group consisting of (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, each of which optionally may be substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, and (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

15 n is 1 or 2;

A is -CR<sup>4</sup>R<sup>5</sup>- or -CHR<sup>a</sup>-CHR<sup>b</sup>-;

R<sup>4</sup> is selected from the group consisting of (i) hydrogen, (ii) (C<sub>1</sub>-C<sub>7</sub>)alkyl, (iii) (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (iv) 4 to 10 member heterocycloalkyl, (v) aryl, optionally substituted with one to three substituents, the substituents being  
20 independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, cyano, carboxy, and carbamoyl, (vi) heteroaryl, optionally substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, cyano, carboxy, and carbamoyl, and (vii)  
25 LR<sup>6</sup>, wherein:

L is selected from the group consisting of -CH<sub>2</sub>-, -NR<sup>7</sup>-, and -O-;

R<sup>6</sup> is aryl, heteroaryl, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, 4 to 10 member heterocycloalkyl, or (C<sub>1</sub>-C<sub>8</sub>)alkoxy, each of which optionally may be  
30 substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-

C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, cyano, carboxy, and carbamoyl; and

R<sup>7</sup> is hydrogen, methyl or ethyl;

R<sup>5</sup> is selected from the group consisting of hydrogen, hydroxyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halogen, and (C<sub>1</sub>-C<sub>6</sub>)alkyl; or R<sup>4</sup> and R<sup>5</sup>, together with the carbon to which they are attached, form a cycloalkyl or heterocycloalkyl ring that optionally incorporates an oxo group and is optionally substituted with (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, halo, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, or (C<sub>1</sub>-C<sub>3</sub>)haloalkyl;

R<sup>a</sup> is (C<sub>1</sub>-C<sub>4</sub>)alkoxy or R<sup>8</sup>-O-C(O)-, wherein R<sup>8</sup> is (C<sub>1</sub>-C<sub>4</sub>)alkyl; and

R<sup>b</sup> is aryl, heteroaryl, or heterocycloalkyl, optionally substituted with halo, (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, or (C<sub>1</sub>-C<sub>3</sub>)haloalkyl; or R<sup>a</sup> and R<sup>b</sup>, together with the carbons to which they are attached, form a cycloalkyl or heterocycloalkyl ring that optionally incorporates an oxo group and is optionally substituted with (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, halo, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, or (C<sub>1</sub>-C<sub>3</sub>)haloalkyl.

In one embodiment of the compounds of formula I, R<sup>1</sup> is selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, optionally substituted 4 to 10 member heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl.

In another embodiment, R<sup>2</sup> is selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, cyano, and cyclopropyl.

In another embodiment, R<sup>4</sup> is selected from the group consisting of (i) hydrogen, (ii) aryl, optionally substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, cyano, carboxy, and carbamoyl, (iii) heteroaryl, optionally substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, cyano, carboxy, and carbamoyl, and (iv) LR<sup>6</sup>, wherein L is selected from the group consisting of -CH<sub>2</sub>-, -NR<sup>7</sup>-, and -O-; and R<sup>6</sup> is aryl or heteroaryl, each of



which optionally may be substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, cyano, carboxy, and carbamoyl.

- 5           In another embodiment, R<sup>4</sup> is as described above, and R<sup>5</sup> is selected from the group consisting of hydrogen, hydroxyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, and (C<sub>1</sub>-C<sub>6</sub>)alkyl; or R<sup>4</sup> and R<sup>5</sup>, together with the carbon to which they are attached, form a cyclic ketone.

- 10           In another embodiment R<sup>a</sup> is as described above, and R<sup>b</sup> is aryl or heteroaryl, optionally substituted with halo, (C<sub>1</sub>-C<sub>3</sub>)alkyl, or (C<sub>1</sub>-C<sub>3</sub>)haloalkyl; or R<sup>a</sup> and R<sup>b</sup>, together with the carbons to which they are attached, form a cycloalkyl or heterocycloalkyl ring that optionally incorporates an oxo group and is optionally substituted with (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, halo, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, or (C<sub>1</sub>-C<sub>3</sub>)haloalkyl.

- 15           Another embodiment of the compounds of formula I includes those compounds wherein R<sup>1</sup> is (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, or phenyl; R<sup>2</sup> is hydrogen; R<sup>3</sup> is selected from the group consisting of isopropyl, cyclobutyl, cyclopentyl, tetrahydrofuranyl, and tetrahydropyranyl; A is -CR<sup>4</sup>R<sup>5</sup>-; and L is -CH<sub>2</sub>- or -O-.

- 20           In other specific embodiments, the invention also relates to the compounds described as Examples 1-175 in the Examples section of the subject application, and pharmaceutically acceptable salts thereof.

- 25           The compounds of the invention have been surprisingly found to show pharmacological activity, including selective inhibition of PDE9, that makes them suitable for the treatment, prevention and/or control of conditions that may be regulated or normalized by inhibition of PDE9.

- 30           The compounds and intermediates of the present invention may be named according to either the IUPAC (International Union for Pure and Applied Chemistry) or CAS (Chemical Abstracts Service, Columbus, OH) nomenclature systems.

#### Definitions

Certain terms used herein are generally defined as follows:

The carbon atom content of the various hydrocarbon-containing moieties herein may be indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety. Thus, for example, (C<sub>1</sub>-  
5 C<sub>6</sub>)alkyl refers to an alkyl group of one to six carbon atoms inclusive.

The term "alkoxy" refers to a straight or branched, monovalent, saturated aliphatic hydrocarbon radical bonded to an oxygen atom that is attached to a core structure. Examples of alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, *tert*-butoxy, pentoxy, and the  
10 like.

The term "alkyl" means a saturated monovalent straight or branched aliphatic hydrocarbon radical. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, *sec*-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, and the like.

15 The term "alkenyl" means a partially unsaturated straight or branched aliphatic hydrocarbon radical having one or more double bonds. Examples of alkenyl groups include ethenyl (also known as "vinyl"), allyl, 1-propenyl, isopropenyl, *n*-butenyl, *n*-pentenyl, and the like. The term "alkenyl" embraces radicals having "*cis*" and "*trans*" orientations, or alternatively, "*Z*" and "*E*"  
20 orientations.

The term "alkynyl" means a partially unsaturated straight or branched aliphatic hydrocarbon radical having one or more triple bonds. Examples of alkynyl groups include 1-propynyl, 2-propynyl (also known as "propargyl"), 1-butynyl, 2-butynyl, 1-pentynyl, and the like.

25 The term "aryl" denotes a monocyclic or polycyclic aromatic ring system, for example, anthracenyl, benzyl, fluorenyl, indenyl, naphthyl, phenanthrenyl, phenyl and the like. The term "aryl" is also intended to include the partially hydrogenated derivatives of such ring systems, e.g. 1,2,3,4-tetrahydronaphthyl.

30 The term "aryloxy" denotes an aryl radical bonded to an oxygen atom that is attached to a core structure, such as benzyloxy.

The terms "carbamoyl" and "carbamyl" denote an amino group ( $--NR'R''$ ) bonded to a carbonyl group ( $C=O$ ) that is attached to a core structure.

The term "cycloalkyl" denotes a saturated monocyclic or bicyclic cycloalkyl group. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like.

The terms "halogen" and "halo" represent chlorine, bromine, fluorine and iodine atoms and radicals.

The term "haloalkyl" refers to an alkyl or cycloalkyl substituent wherein at least one hydrogen radical is replaced with a halogen radical. Where more than one hydrogen is replaced with halogen, the halogens may be the same or different. Examples of haloalkyl radicals include trifluoromethyl, 2,2,2-trifluoroethyl, 4,4,4-trifluorobutyl, 4,4-difluorocyclohexyl, chloromethyl, dichloromethyl, trichloromethyl, 1-bromoethyl, and the like.

The term "haloalkoxy" refers to an alkoxy radical in which at least one hydrogen radical is replaced with a halogen radical. Where more than one hydrogen is replaced with halogen, the halogens may be the same or different. Examples of haloalkoxy radicals include difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, chloromethoxy, bromomethoxy, and the like.

The term "heteroaryl" as used herein includes heterocyclic unsaturated ring systems containing one or more heteroatoms such as nitrogen, oxygen, and sulfur. If the heteroaryl group contains more than one heteroatom, the heteroatoms may be the same or different. The heteroaryl radicals may be bonded via a carbon atom or a heteroatom. The term "heteroaryl" is also intended to include the partially hydrogenated derivatives of such ring systems. Examples of heteroaryl groups include furanyl (also known as "furyl"), imidazolynyl, imidazolyl (also known as "1,3-diazolyl"), indolyl, oxadiazolyl, oxazinyl, oxazolyl, isoxazolyl, pyranyl, pyrazinyl (also known as "1,4-diazinyl"), pyrazolyl (also known as "1,2-diazolyl"), pyrazolynyl, pyrazyl, pyridazinyl (also known as "1,2-diazinyl"), pyridyl (also known as pyridinyl), pyrimidinyl (also known as "1,3-diazinyl" and "pyrimidyl"), pyrrolyl, thiadiazinyl,

thiadiazolyl, thiatriazolyl, thiazolyl, isothiazolyl, thienyl, thiofuranyl (also known as "thiophenyl"), thiopyranyl, triazinyl, triazolyl, and the like.

The term "heteroaryl" also embraces radicals in which 2 or 3 rings are fused together, wherein at least on such ring contains a heteroatom as a ring atom, including radicals wherein (a) a heterocycloalkyl (or heterocyclic ketone) ring is fused with an aryl or heteroaryl ring, or (b) a cycloalkyl (or cyclic ketone) ring is fused with a heteroaryl ring. Examples of 2-fused ring heteroaryls include benzodioxinyl, dihydrobenzodioxinyl, benzofuranyl, dihydrobenzofuranyl, isobenzofuranyl, benzimidazolyl, benzothiadiazolyl, tetrahydrobenzothiadiazolyl, benzothiazolyl, benzothienyl (also known as "benzothiophenyl," "thionaphthenyl," and "benzothiofuranyl"), benzoxazinyl, dihydrobenzoxazinyl, benzoxazolyl, chromanyl, isochromanyl, chromenyl, cinnolyl (also known as "1,2-benzodiazinyl"), imidazopyridinyl (e.g. imidazo[1,2-a]pyridinyl or imidazo[4,5-c]pyridinyl), indazolyl, indolyl, isoindolyl, indolizyl, indolyl, isoindolyl, naphthyridinyl, oxathiolopyrrolyl, pteridinyl, pthalazinyl, purinyl (also known as "imidazo[4,5-d]pyrimidinyl"), pyranopyrrolyl, pyrazoloazepinyl, tetrahydropyrazoloazepinyl (e.g. tetrahydropyrazolo[1,5-a]azepinyl), pyrazolopyridinyl, tetrahydropyrazolopyridinyl (e.g. tetrahydropyrazolo[1,5-a]pyridinyl), pyrazolopyrimidinyl (e.g. pyrazolo[3,4-d]pyrimidinyl), pyridopyrazinyl (e.g. pyrido[2,3-b]pyrazinyl), pyridopyridinyl, pyrrolopyrazolyl, dihydropyrrolopyrazolyl (e.g. dihydropyrrolo[1,2-b]pyrazolyl), quinazolinyl (also known as "1,3-benzodiazinyl"), quinolyl (also known as "1-benzazinyl"), isoquinolyl (also known as "2-benzazinyl"), quinolizyl, quinolyl, isoquinolyl, quinoxalinyl, dithianaphthalenyl, thienofuranyl (e.g. thieno[3,2-b]furanyl), and the like.

Examples of 3-fused ring heteroaryls include acridinyl, diazaanthryl, triazaphenanthrene, carbazolyl, carbolinyl, furocinnolyl, perimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, thianthrenyl, xanthenyl, and the like.

The term "heterocycloalkyl" denotes a saturated monocyclic or polycyclic cycloalkyl group, in which at least one of the carbon atoms is replaced with a heteroatom such as nitrogen, oxygen or sulfur. If the heterocycle contains more than one heteroatom, the heteroatoms may be the same or different. The heterocycloalkyl radicals may be bonded via a carbon atom or a heteroatom. Preferably, the heterocycloalkyl radical has 4 to 10 members. Examples of heterocycloalkyl groups include azetidiny, dioxacyclohexyl, 1,3-dioxolanyl, imidazolidiny, morpholiny, piperaziny, piperidiny, pyrazolidiny, pyrrolidiny, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thiazanyl, and the like.

A cyclic group may be bonded to another group in more than one way. If no particular bonding arrangement is specified, then all possible arrangements are intended. For example, the term "pyridyl" includes 2-, 3- or 4-pyridyl (2-, 3-, or 4-pyridiny).

The term "mammal" means animals including, for example, dogs, cats, cows, sheep, goats, horses and humans. Preferred mammals include humans.

The term "oxo" means a carbonyl (C=O) group formed by the combination of a carbon atom and an oxygen atom.

The term "patient" includes both human and non-human patients.

The phrase "pharmaceutically acceptable" indicates that the designated carrier, vehicle, diluent, and/or salt is generally chemically and/or physically compatible with the other ingredients comprising the formulation, and physiologically compatible with the recipient thereof.

The term "salts" refers to both organic and inorganic salts of a compound of Formula (I). Such salts can be prepared *in situ* during the final isolation and purification of a compound, or by separately reacting a compound, prodrug or stereoisomer of Formula (I) with a suitable organic or inorganic acid or base and isolating the salt thus formed. Representative anionic salts include bromide, chloride, iodide, sulfate, bisulfate, nitrate, acetate, trifluoroacetate, oxalate, besylate, palmitate, pamoate, malonate,

stearate, laurate, malate, borate, benzoate, lactate, phosphate, hexafluorophosphate, benzene sulfonate, tosylate, formate, citrate, maleate, fumarate, succinate, tartrate, naphthoate, naphthalate, mesylate, glucoheptonate, lactobionate and laurylsulphonate salts and the like.

- 5 Representative cationic salts include sodium, potassium, calcium, and magnesium salts and the like. See generally, *e.g.*, Berge, et al., *J. Pharm. Sci.*, 66, 1-19 (1977).

A salt of a compound of Formula (I) may be readily prepared by mixing together solutions of a compound of Formula (I) and the desired acid or base,  
10 as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

The term "radical" denotes a group of atoms that behaves as a single reactant in a chemical reaction, *e. g.*, an organic radical is a group of atoms that imparts characteristic properties to a compound containing it, or which  
15 remains unchanged during a series of reactions or transformations.

The phrase "reaction-inert solvent" or "inert solvent" refers to a solvent, or mixture of solvents, that does not interact with starting materials, reagents, intermediates or products in a manner that adversely affects their desired properties.

20 The terms "treat," "treating," "treated" or "treatment" as used herein includes preventative (*e.g.*, prophylactic), palliative or curative uses or results.

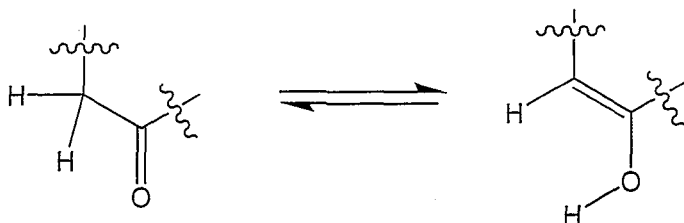
The compounds of Formula (I) may contain asymmetric or chiral centers and, therefore, exist in different stereoisomeric forms. Those skilled in the art will appreciate that, unless otherwise specified, all stereoisomers (*e.g.*,  
25 enantiomers and diastereoisomers, and racemic mixtures thereof) of the novel compounds and intermediates described, illustrated and/or discussed herein are within the scope of the claimed invention. In addition, unless otherwise specified, the present invention embraces all geometric and positional isomers.

30 Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods

well-known to those of ordinary skill in the art, such as 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., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Additional methods include resolution of racemic mixtures using chiral salts, as well as chiral chromatography.

Those skilled in the art will further recognize that the compounds of Formula (I) can exist in crystalline form as hydrates wherein molecules of water are incorporated within the crystal structure thereof and as solvates wherein molecules of a solvent are incorporated therein. All such hydrate and solvate forms are considered part of this invention.

Practitioners will appreciate that certain compounds of Formula (I) may exist as tautomeric isomers, i.e., that equilibrium exists between two isomers which are in rapid equilibrium with each other. A common example of tautomerism is keto-enol tautomerism, i.e.,



The degree to which one tautomer is present over the other depends upon various factors, including substitution pattern and solvent type. Other examples in accordance with the present invention will be recognized by those skilled in the art. All tautomeric forms of Formula (I) are included within the scope of the invention unless otherwise specified.

The present invention also embraces isotopically-labeled compounds of Formula (I) that are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of Formula (I) include isotopes of hydrogen, carbon, nitrogen, oxygen, sulfur,

phosphorus, fluorine, and chlorine, such as  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{17}\text{O}$ ,  $^{35}\text{S}$ ,  $^{18}\text{F}$  and  $^{36}\text{Cl}$ , respectively. The compounds of Formula (I), and pharmaceutically acceptable salts thereof, that contain the aforementioned isotopes and/or other isotopes of the other atoms are within the scope of the  
5 instant invention.

Certain isotopically-labeled compounds of Formula (I), for example those into which radioactive isotopes such as  $^3\text{H}$  and  $^{14}\text{C}$  are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e.  $^3\text{H}$ , and  $^{14}\text{C}$  isotopes are particularly preferred for their ease of preparation and  
10 detectability. Furthermore, substitution with heavier isotopes such as deuterium, i.e.  $^2\text{H}$ , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life, or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically-labeled compounds of Formula (I), and pharmaceutically  
15 acceptable salts thereof, can be generally prepared by carrying out analogous procedures to those disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically-labeled reagent for a non-isotopically labeled reagent.

The invention also includes pharmaceutical compositions comprising  
20 an amount of a compound of Formula (I), or a pharmaceutically acceptable salt of the compound, and optionally a pharmaceutically acceptable vehicle, carrier or diluent. In a preferred embodiment, the pharmaceutical composition is of an amount effective at inhibiting the enzyme PDE9 in a mammal. In another preferred embodiment, the mammal is a human.

25 The present invention includes the use of a combination of a PDE9 inhibitor compound as provided in Formula (I) and one or more additional pharmaceutically active agent(s). If a combination of active agents is administered, then they may be administered sequentially or simultaneously, in separate dosage forms or combined in a single dosage form. Accordingly,  
30 the present invention also includes pharmaceutical compositions comprising an amount of: (a) a first agent comprising a compound of Formula (I) or a



pharmaceutically acceptable salt of the compound; (b) a second pharmaceutically active agent; and (c) a pharmaceutically acceptable carrier, vehicle or diluent.

Various pharmaceutically active agents may be selected for use in conjunction with the compounds of Formula (I), depending on the disease, disorder, or condition to be treated. Pharmaceutically active agents that may be used in combination with the compositions of the present invention include, without limitation:

(i) acetylcholinesterase inhibitors, such as donepezil hydrochloride (ARICEPT, MEMAC), physostigmine salicylate (ANTILIRIUM), physostigmine sulfate (ESERINE), metrifonate, neostigmine, ganstigmine, pyridostigmine (MESTINON), ambenonium (MYTELASE), demarcarium, Debio 9902 (also known as ZT-1; Debiopharm), rivastigmine (EXELON), ladostigil, NP-0361, galantamine hydrobromide (RAZADYNE, RIMINYL, NIVALIN), tacrine (COGNEX), tolserine, velnacrine maleate, memoquin, huperzine A (HUP-A; NeuroHitech), phenserine, and edrophonium (ENLON, TENSILON);

(ii) amyloid- $\beta$  (or fragments thereof), such as A $\beta$ <sub>1-15</sub> conjugated to pan HLA DR-binding epitope (PADRE), ACC-001 (Elan/Wyeth), ACI-01, ACI-24, AN-1792, Affitope AD-01, CAD106, and V-950;

(iii) antibodies to amyloid- $\beta$  (or fragments thereof), such as bapineuzumab (also known as AAB-001), AAB-002 (Wyeth/Elan), ACI-01-Ab7, BAN-2401, intravenous Ig (GAMMAGARD), LY2062430 (humanized m266; Lilly), PF-04360365 (also known as RN-1219; Pfizer), RN-6G (Pfizer), R1450 (Roche), ACU-5A5, huC091, and those disclosed in International Patent Publication Nos WO04/032868, WO05/025616, WO06/036291, WO06/069081, WO06/118959, in US Patent Publication Nos US2003/0073655, US2004/0192898, US2005/0048049, US2005/0019328, in European Patent Publication Nos EP0994728 and 1257584, and in US Patent No 5,750,349;

(iv) amyloid-lowering or -inhibiting agents (including those that reduce amyloid production, accumulation and fibrillization) such as colostrinin,

bisnorcymserine (also known as BNC), NIC5-15 (Humanetics), E-2012 (Eisai), pioglitazone, clioquinol (also known as PBT1), PBT2 (Prana Biotechnology), flurbiprofen (ANSAID, FROBEN) and its *R*-enantiomer tarenflurbil (FLURIZAN), nitroflurbiprofen, fenoprofen (FENOPRON, NALFON), ibuprofen (ADVIL, MOTRIN, NUROFEN), ibuprofen lysinate, meclofenamic acid, meclofenamate sodium (MECLOMEN), indomethacin (INDOCIN), diclofenac sodium (VOLTAREN), diclofenac potassium, sulindac (CLINORIL), sulindac sulfide, diflunisal (DOLOBID), naproxen (NAPROSYN), naproxen sodium (ANAPROX, ALEVE), ARC031 (Archer Pharmaceuticals), CAD-106 (Cytos), LY450139 (Lilly), insulin-degrading enzyme (also known as insulysin), the ginkgo biloba extract EGb-761 (ROKAN, TEBONIN), tramiprosate (CEREBRIL, ALZHEMED), eprodinate (FIBRILLEX, KIACTA), compound W (3,5-bis(4-nitrophenoxy)benzoic acid), NGX-96992, neprilysin (also known as neutral endopeptidase (NEP)), scyllo-inositol (also known as scyllitol), atorvastatin (LIPITOR), simvastatin (ZOCOR), KLVFF-(EEX)<sub>3</sub>, SKF-74652, ibutamoren mesylate, and RAGE (receptor for advanced glycation end-products) inhibitors, such as TTP488 (also known as PF-4494700; Transtech) and TTP4000 (Transtech), and those disclosed in US Patent No 7,285,293, including PTI-777;

(v) alpha-adrenergic receptor agonists, such as clonidine (CATAPRES), metaraminol (ARAMINE), methyldopa (ALDOMET, DOPAMET, NOVOMEDOPA), tizanidine (ZANAFLEX), phenylephrine (also known as neosynephrine), methoxamine, cirazoline, guanfacine (INTUNIV), lofexidine, xylazine, modafinil (PROVIGIL), adrafinil, and armodafinil (NUVIGIL);

(vi) beta-adrenergic receptor blocking agents (beta blockers), such as carteolol, esmolol (BREVIBLOC), labetalol (NORMODYNE, TRANDATE), oxprenolol (LARACOR, TRASACOR), pindolol (VISKEN), propranolol (INDERAL), sotalol (BETAPACE, SOTALAX, SOTACOR), timolol (BLOCADREN, TIMOPTIC), acebutolol (SECTRAL, PRENT), nadolol (CORCARD), metoprolol tartrate (LOPRESSOR), metoprolol succinate (TOPROL-XL), atenolol (TENORMIN), butoxamine, and SR 59230A (Sanofi);

(vii) anticholinergics, such as amitriptyline (ELAVIL, ENDEP), butriptyline, benztropine mesylate (COGENTIN), trihexyphenidyl (ARTANE), diphenhydramine (BENADRYL), orphenadrine (NORFLEX), hyoscyamine, atropine (ATROPEN), scopolamine (TRANSDERM-SCOP), scopolamine  
5 methylbromide (PARMINE), dicycloverine (BENTYL, BYCLOMINE, DIBENT, DILOMINE, tolterodine (DETROL), oxybutynin (DITROPAN, LYRINEL XL, OXYTROL), penthienate bromide, propantheline (PRO-BANTHINE), cyclizine, imipramine hydrochloride (TOFRANIL), imipramine maleate (SURMONTIL), lofepramine, desipramine (NORPRAMIN), doxepin (SINEQUAN, ZONALON),  
10 trimipramine (SURMONTIL), and glycopyrrolate (ROBINUL);

(viii) anticonvulsants, such as carbamazepine (TEGRETOL, CARBATROL), oxcarbazepine (TRILEPTAL), phenytoin sodium (PHENYTEK), fosphenytoin (CEREBYX, PRODILANTIN), divalproex sodium (DEPAKOTE), gabapentin (NEURONTIN), pregabalin (LYRICA), topiramate  
15 (TOPAMAX), valproic acid (DEPAKENE), valproate sodium (DEPACON), 1-benzyl-5-bromouracil, progabide, beclamide, zonisamide (TRERIEF, EXCEGRAN), CP-465022, retigabine, talampanel, and primidone (MYSOLINE);

(ix) antipsychotics, such as lurasidone (also known as SM-13496; Dainippon Sumitomo), aripiprazole (ABILIFY), chlorpromazine  
20 (THORAZINE), haloperidol (HALDOL), iloperidone (FANAPTA), flupentixol decanoate (DEPIXOL, FLUANXOL), reserpine (SERPLAN), pimozide (ORAP), fluphenazine decanoate, fluphenazine hydrochloride, prochlorperazine (COMPRO), asenapine (SAPHRIS), abaperidone, loxapine  
25 (LOXITANE), mesoridazine, molindone (MOBAN), perphenazine, thioridazine, thiothixine, trifluoperazine (STELAZINE), clozapine (CLOZARIL), norclozapine (ACP-104), risperidone (RISPERDAL), paliperidone (INVEGA), melperone, olanzapine (ZYPREXA), quetiapine (SEROQUEL), sertindole, sulpiride (MERESA, DOGMATYL, SULPITIL), talnetant, amisulpride, ziprasidone  
30 (GEODON), blonanserin (LONASEN), ACP-103 (Acadia Pharmaceuticals), and bifeprunox;

(x) calcium channel blockers such as nilvadipine (ESCOR, NIVADIL),  
diperdipine, amlodipine (NORVASC, ISTIN, AMLODIN), felodipine  
(PLENDIL), nicardipine (CARDENE), nifedipine (ADALAT, PROCARDIA),  
MEM 1003 and its parent compound nimodipine (NIMOTOP), nisoldipine  
5 (SULAR), nitrendipine, lacidipine (LACIPIL, MOTENS), lercanidipine  
(ZANIDIP), lifarizine, diltiazem (CARDIZEM), verapamil (CALAN, VERELAN),  
AR-R 18565 (AstraZeneca), and enecadin;

(xi) catechol O-methyltransferase (COMT) inhibitors, such as  
tolcapone (TASMAR), entacapone (COMTAN), and tropolone;

10 (xii) central nervous system stimulants, such as caffeine,  
phenmetrazine, phendimetrazine, pemoline, fencamfamine  
(GLUCOENERGAN, REACTIVAN), fenethylamine (CAPTAGON), pipradol  
(MERETRAN), deanol (also known as dimethylaminoethanol),  
methylphenidate (DAYTRANA), methylphenidate hydrochloride (RITALIN),  
15 dexamethylphenidate (FOCALIN), amphetamine (alone or in combination with  
other CNS stimulants, e.g. ADDERALL (amphetamine aspartate,  
amphetamine sulfate, dextroamphetamine saccharate, and  
dextroamphetamine sulfate)), dextroamphetamine sulfate (DEXEDRINE,  
DEXTROSTAT), methamphetamine (DESOXYN), lisdexamfetamine  
20 (VYVANSE), and benzphetamine (DIDREX);

(xiii) corticosteroids, such as prednisone (STERAPRED,  
DELTASONE), prednisolone (PRELONE), prednisolone acetate (OMNIPRED,  
PRED MILD, PRED FORTE), prednisolone sodium phosphate (ORAPRED  
ODT), methylprednisolone (MEDROL); methylprednisolone acetate (DEPO-  
25 MEDROL), and methylprednisolone sodium succinate (A-METHAPRED,  
SOLU-MEDROL);

(xiv) dopamine receptor agonists, such as apomorphine (APOKYN),  
bromocriptine (PARLODEL), cabergoline (DOSTINEX), dihydrexidine,  
dihydroergocryptine, fenoldopam (CORLOPAM), lisuride (DOPERGIN),  
30 pergolide (PERMAX), priribedil (TRIVASTAL, TRASTAL), pramipexole

(MIRAPEX), quinpirole, ropinirole (REQUIP), rotigotine (NEUPRO), SKF-82958 (GlaxoSmithKline), and sarizotan;

(xv) dopamine receptor antagonists, such as tetrabenazine (NITOMAN, XENAZINE), 7-hydroxyamoxapine, droperidol (INAPSINE, DRIDOL, DROPLETAN), domperidone (MOTILIUM), L-741742, L-745870, raclopride, SB-277011A, SCH-23390, ecopipam, SKF-83566, and metoclopramide (REGLAN);

(xvi) dopamine reuptake inhibitors such as nomifensine maleate (MERITAL), vanoxerine (also known as GBR-12909) and its decanoate ester DBL-583, and amineptine;

(xvii) gamma-amino-butyric acid (GABA) receptor agonists, such as baclofen (LIORESAL, KEMSTRO), siclofen, pentobarbital (NEMBUTAL), progabide (GABRENE), and clomethiazole;

(xviii) histamine 3 (H3) antagonists such as ciproxifan and those disclosed in US Patent Publication Nos US2005-0043354, US2005-0267095, US2005-0256135, US2008-0096955, US2007-1079175, and US2008-0176925; International Patent Publication Nos WO2006/136924, WO2007/063385, WO2007/069053, WO2007/088450, WO2007/099423, WO2007/105053, WO2007/138431, and WO2007/088462; and US Patent No 7,115,600;

(xix) immunomodulators such as glatiramer acetate (also known as copolymer-1; COPAXONE), MBP-8298 (synthetic myelin basic protein peptide), dimethyl fumarate, fingolimod (also known as FTY720), roquinimex (LINOMIDE), laquinimod (also known as ABR-215062 and SAIK-MS), ABT-874 (human anti-IL-12 antibody; Abbott), rituximab (RITUXAN), alemtuzumab (CAMPATH), daclizumab (ZENAPAX), and natalizumab (TYSABRI);

(xx) immunosuppressants such as methotrexate (TREXALL, RHEUMATREX), mitoxantrone (NOVANTRONE), mycophenolate mofetil (CELLCEPT), mycophenolate sodium (MYFORTIC), azathioprine (AZASAN, IMURAN), mercaptopurine (PURI-NETHOL), cyclophosphamide (NEOSAR, CYTOXAN), chlorambucil (LEUKERAN), cladribine (LEUSTATIN, MYLINAX);

alpha-fetoprotein, etanercept (ENBREL), and 4-benzyloxy-5-((5-undecyl-2H-pyrrol-2-ylidene)methyl)-2,2'-bi-1H-pyrrole (also known as PNU-156804);

(xxi) interferons, including interferon beta-1a (AVONEX, REBIF) and interferon beta-1b (BETASERON, BETAFERON);

5 (xxii) levodopa (or its methyl or ethyl ester), alone or in combination with a DOPA decarboxylase inhibitor (e.g. carbidopa (SINEMET, CARBILEV, PARCOPA), benserazide (MADOPAR),  $\alpha$ -methyldopa, monofluromethyldopa, difluoromethyldopa, brocresine, or *m*-hydroxybenzylhydrazine);

(xxiii) *N*-methyl-D-aspartate (NMDA) receptor antagonists, such as  
10 memantine (NAMENDA, AXURA, EBIXA), amantadine (SYMMETREL),  
acamprosate (CAMPRAL), besonprodil, ketamine (KETALAR), delucemine,  
dexanabinol, dexefaroxan, dextromethorphan, dextropropanolol, CP-  
283097, himantane, idantadol, ipenoxazone, L-701252 (Merck), lamicemine,  
levorphanol (DROMORAN), LY-233536 and LY-235959 (both Lilly),  
15 methadone, (DOLOPHINE), neramexane, perzinfotel, phencyclidine,  
tianeptine (STABLON), dizocilpine (also known as MK-801), EAB-318  
(Wyeth), ibogaine, voacangine, tiletamine, riluzole (RILUTEK), aptiganel  
(CERES0TAT), gavestinel, and remacimide;

(xxiv) monoamine oxidase (MAO) inhibitors, such as selegiline  
20 (EMSAM), selegiline hydrochloride (l-deprenyl, ELDEPRYL, ZELAPAR),  
dimethylselegiline, brofaromine, phenelzine (NARDIL), tranlycypromine  
(PARNATE), moclobemide (AURORIX, MANERIX), befloxatone, safinamide,  
isocarboxazid (MARPLAN), nialamide (NIAMID), rasagiline (AZILECT),  
iproniazide (MARSILID, IPROZID, IPRONID), CHF-3381 (Chiesi  
25 Farmaceutici), iproclozide, toloxatone (HUMORYL, PERENUM), bifemelane,  
desoxypeganine, harmine (also known as telepathine or banasterine),  
harmaline, linezolid (ZYVOX, ZYVOXID), and pargyline (EUDATIN,  
SUPIRDYL);

(xxv) muscarinic receptor (particularly M1 subtype) agonists, such as  
30 bethanechol chloride (DUVOID, URECHOLINE), itameline, pilocarpine  
(SALAGEN), NGX267, arecoline, L-687306 (Merck), L-689660 (Merck),

furtrethonium iodide (FURAMON, FURANOL), furtrethonium benzensulfonate, furtrethonium *p*-toluenesulfonate, McN-A-343, oxotremorine, sabcomeline, AC-90222 (Acadia Pharmaceuticals), and carbachol (CARBASTAT, MIOSTAT, CARBOPTIC);

5 (xxvi) neuroprotective drugs such as 2,3,4,9-tetrahydro-1*H*-carbazol-3-one oxime, desmoteplase, anatibant, astaxanthin, neuropeptide NAP (e.g. AL-108 and AL-208; both Allon Therapeutics), neurostrol, perampnenel, ispronidine, bis(4- $\beta$ -D-glucopyranosyloxybenzyl)-2- $\beta$ -D-glucopyranosyl-2-isobutyltartrate (also known as dactylorhin B or DHB), formobactin, xaliproden  
10 (XAPRILA), lactacystin, dimeboline hydrochloride (DIMEBON), disufenton (CEROVIVE), arundic acid (ONO-2506, PROGLIA, CEREACT), citicoline (also known as cytidine 5'-diphosphocholine), edaravone (RADICUT), AEOL-10113 and AEOL-10150 (both Aeolus Pharmaceuticals), AGY-94806 (also known as SA-450 and Msc-1), granulocyte-colony stimulating factor (also  
15 known as AX-200), BAY-38-7271 (also known as KN-387271; Bayer AG), ancrod (VIPRINEX, ARWIN), DP-b99 (D-Pharm Ltd), HF-0220 (17- $\beta$ -hydroxyepiandrosterone; Newron Pharmaceuticals), HF-0420 (also known as oligotropin), pyridoxal 5'-phosphate (also known as MC-1), microplasmin, S-18986, piclozotan, NP031112, tacrolimus, L-seryl-L-methionyl-L-alanyl-L-  
20 lysyl-L-glutamyl-glycyl-L-valine, AC-184897 (Acadia Pharmaceuticals), ADNF-14 (National Institutes of Health), stilbazulenyl nitron, SUN-N8075 (Daiichi Sunitory Biomedical Research), and zonampanel;

(xxvii) nicotinic receptor agonists, such as epibatidine, ABT-089 (Abbott), ABT-594, AZD-0328 (AstraZeneca), EVP-6124, R3487 (also known  
25 as MEM3454; Roche/Memory Pharmaceuticals), R4996 (also known as MEM63908; Roche/Memory Pharmaceuticals), TC-4959 and TC-5619 (both Targacept), and RJR-2403;

(xxviii) norepinephrine (noradrenaline) reuptake inhibitors, such as atomoxetine (STRATTERA), doxepin (APONAL, ADAPIN, SINEQUAN),  
30 nortriptyline (AVENTYL, PAMELOR, NORTRILEN), amoxapine (ASENDIN, DEMOLOX, MOXIDIL), reboxetine (EDRONAX, VESTRA), viloxazine

(VIVALAN), maprotiline (DEPRILEPT, LUDIOMIL, PSYMION), bupropion (WELLBUTRIN), and radaxafine;

(xxix) other PDE9 inhibitors, such as BAY 73-6691 (Bayer AG) and those disclosed in US Patent Publication Nos US2003/0195205, 5 US2004/0220186, US2006/0111372, US2006/0106035, and USSN 12/118,062 (filed May 9, 2008);

(xxx) other phosphodiesterase (PDE) inhibitors, including (a) PDE1 inhibitors (e.g. vinpocetine (CAVINTON, CERACTIN, INTELECTOL) and those disclosed in US Patent No 6,235,742, (b) PDE2 inhibitors (e.g. erythro- 10 9-(2-hydroxy-3-nonyl)adenine (EHNA), BAY 60-7550, and those described in US Patent No. 6,174,884), (c) PDE4 inhibitors (e.g. rolipram, Ro 20-1724, ibudilast (KETAS), piclamilast (also known as RP73401), CDP840, cilomilast (ARIFLO), roflumilast, tofimilast, oglemilast (also known as GRC 3886), tetomilast (also known as OPC-6535), lirimifast, theophylline (UNIPHYL, 15 THEOLAIR), arofylline (also known as LAS-31025), doxofylline, RPR-122818, or mesembrine), and (d) PDE5 inhibitors (e.g. sildenafil (VIAGRA, REVATIO), tadalafil (CIALIS), vardenafil (LEVITRA, VIVANZA), udenafil, avanafil, dipyridamole (PERSANTINE), E-4010, E-4021, E-8010, zaprinast, PF-489791 (Pfizer), UK-357903 (Pfizer), DA-8159, and those disclosed in International 20 Patent Applications WO2002/020521, WO2005/049616, WO2006/120552, WO2006/126081, WO2006/126082, WO2006/126083, and WO2007/122466);

(xxxi) quinolines, such as quinine (including its hydrochloride, dihydrochloride, sulfate, bisulfate and gluconate salts), chloroquine, 25 sontoquine, hydroxychloroquine (PLAQUENIL), mefloquine (LARIAM), and amodiaquine (CAMOQUIN, FLAVOQUINE);

(xxxii)  $\beta$ -secretase inhibitors, such as WY-25105, (+)-phenserine tartrate (POSIPHEN), LSN-2434074 (also known as LY-2434074), PNU-33312, KMI-574, SCH-745966, Ac-rER ( $N^2$ -acetyl-D-arginyl-L-arginine), loxistatin (also known as E64d), and CA074Me;



(xxxiii)  $\gamma$ -secretase inhibitors, such as LY-411575 (Lilly), LY-685458 (Lilly), ELAN-G, ELAN-Z, 4-chloro-*N*-[2-ethyl-1(*S*)-(hydroxymethyl)butyl]benzenesulfonamide;

(xxxiv) serotonin (5-hydroxytryptamine) 1A (5-HT<sub>1A</sub>) receptor antagonists, such as spiperone, *levo*-pindolol, BMY 7378, NAD-299, *S*(-)-UH-301, NAN 190, WAY 100635, lecozotan (also known as SRA-333; Wyeth);

(xxxv) serotonin (5-hydroxytryptamine) 4 (5-HT<sub>4</sub>) receptor agonists, such as PRX-03140 (Epix);

(xxxvi) serotonin (5-hydroxytryptamine) 6 (5-HT<sub>6</sub>) receptor antagonists, such as mianserin (TORVOL, BOLVIDON, NORVAL), methiothepin (also known as metitepine), ritanserin, ALX-1161, ALX-1175, MS-245, LY-483518 (also known as SGS518; Lilly), MS-245, Ro 04-6790, RO 43-68544, Ro 63-0563, RO 65-7199, Ro 65-7674, SB-399885, SB-214111, SB-258510, SB-271046, SB-357134, SB-699929, SB-271046, SB-742457 (GlaxoSmithKline), Lu AE58054 (Lundbeck A/S), and PRX-07034 (Epix);

(xxxvii) serotonin (5-HT) reuptake inhibitors such as alaproclate, citalopram (CELEXA, CIPRAMIL), escitalopram (LEXAPRO, CIPRALEX), clomipramine (ANAFRANIL), duloxetine (CYMBALTA), femoxetine (MALEXIL), fenfluramine (PONDIMIN), norfenfluramine, fluoxetine (PROZAC), fluvoxamine (LUVOX), indalpine, milnacipran (IXEL), paroxetine (PAXIL, SEROXAT), sertraline (ZOLOFT, LUSTRAL), trazodone (DESYREL, MOLIPAXIN), venlafaxine (EFFEXOR), zimelidine (NORMUD, ZELMID), bicifadine, desvenlafaxine (PRISTIQ), brasofensine, and tesofensine;

(xxxviii) trophic factors, such as nerve growth factor (NGF), basic fibroblast growth factor (bFGF; ERSOFERMIN), neurotrophin-3 (NT-3), cardiotrophin-1, brain-derived neurotrophic factor (BDNF), neublastin, meteorin, and glial-derived neurotrophic factor (GDNF), and agents that stimulate production of trophic factors, such as propentofylline, idebenone, PYM50028 (COGANE; Phytopharm), and AIT-082 (NEOTROFIN);

and the like.

The invention also includes methods of inhibiting PDE9 in a mammal comprising administering to the mammal in need of such inhibition a PDE9 inhibiting amount of: (a) a compound of Formula (I), or a pharmaceutically acceptable salt thereof; or (b) a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable vehicle, carrier or diluent; either alone or in combination with a second agent as described above.

The invention also includes methods of treating conditions mediated by PDE9 inhibition in a mammal comprising administering to the mammal in need of such treatment a therapeutically effective amount of: (a) a compound of Formula (I), or a pharmaceutically acceptable salt thereof; or (b) a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable vehicle, carrier or diluent; either alone or in combination with a second agent described above.

Conditions that may be treated, controlled or prevented by the methods of the present invention include diseases and disorders associated with neurodegeneration such as: Alexander disease, Alper's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS; also known as Lou Gehrig's disease or motor neuron disease), ataxia-telangiectasia, Batten disease (also known as Spielmeyer-Vogt-Sjogren-Batten disease), Binswanger's dementia (subcortical arteriosclerotic encephalopathy), bipolar disorders, bovine spongiform encephalopathy (BSE), Canavan disease, chemotherapy-induced dementia, Cockayne syndrome, corticobasal degeneration, Creutzfeldt-Jakob disease, depression, Down syndrome, frontotemporal lobar degeneration (including frontotemporal dementia, semantic dementia, and progressive nonfluent aphasia), Gerstmann-Straüssler-Scheinker disease, glaucoma, Huntington's disease (chorea), HIV-associated dementia, hyperkinesias, Kennedy's disease, Korsakoff's syndrome (amnesic-confabulatory syndrome), Krabbe's disease, Lewy body dementia, logopenic progressive aphasia, Machado-Joseph disease (spinocerebellar ataxia type 3), multiple sclerosis,

multiple system atrophy (olivopontocerebellar atrophy), myasthenia gravis, Parkinson's disease, Pelizaeus-Merzbacher disease, Pick's disease, pre-senile dementia (mild cognitive impairment), primary lateral sclerosis, primary progressive aphasia, radiation-induced dementia, Refsum's disease (phytanic  
5 acid storage disease), Sandhoff disease, Schilder's disease, schizophrenia, semantic dementia, senile dementia, Shy-Drager syndrome, spinocerebellar ataxias, spinal muscular atrophies, Steele-Richardson-Olszewski disease (progressive supranuclear palsy), tabes dorsalis, tardive dyskinesia, vascular amyloidosis, and vascular dementia (multi-infarct dementia).

10 Preferably the neurodegenerative disease or disorder is Alzheimer's disease.

Other conditions and disorders associated with PDE9 that may be treated or controlled by the methods of the present invention include disorders of the urogenital system such as sexual dysfunction, attention deficit disorder  
15 (ADD), attention deficit hyperactivity disorder (ADHD), diabetes, cardiovascular disorders or diseases such as systemic hypertension, pulmonary hypertension, congestive heart failure, coronary artery disease, atherosclerosis, stroke, thrombosis, conditions of reduced blood vessel patency (e.g. post-percutaneous transluminal coronary angioplasty),  
20 peripheral vascular disease, renal disease, angina (including stable, unstable, and variant (Prinzmetal) angina), and any condition where improved blood flow leads to improved end organ function.

The present invention also relates to methods for promoting neurorestoration and functional recovery in patients suffering from traumatic  
25 or non-traumatic injury to the brain, spinal cord or peripheral nerves. Traumatic brain injuries include both closed head injuries (in which the skull is not broken) and open, or penetrating, head injuries (in which an object pierces the skull and breaches the dura mater), wherein sudden trauma (e.g., accidents, falls, assaults) causes damage to the brain tissue by tearing,  
30 stretching, bruising, or swelling. Causes of non-traumatic brain injuries include aneurism, stroke, meningitis, oxygen deprivation due to anoxia,

hypoxia, or ischemia, brain tumor, infection (e.g. encephalitis), poisoning, substance abuse, and the like. The present invention is useful for the treatment of cognitive impairment and cognitive dysfunction resulting from brain injuries as well as from neurodegenerative diseases and disorders.

5           The present invention also relates to methods for preventing the above-described conditions in a mammal, including human, comprising the steps of administering to the mammal an amount of: (a) a compound of Formula (I), or a pharmaceutically acceptable salt thereof; or (b) a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable vehicle, carrier or  
10           diluent; either alone or in combination with a second agent as described above, as part of an appropriate dosage regimen designed to prevent said condition.

          The present invention also relates to methods for enhancing cognition  
15           and for improving cognitive deficits, including deficits in perception, concentration, learning, memory, communication, reasoning, and problem-solving.

          The appropriate dosage regimen, the amount of each dose administered and the intervals between doses of the compound will depend  
20           upon, among other considerations, the compound of Formula (I) of this invention being used, the type of pharmaceutical composition being used, the characteristics of the subject being treated and the type and severity of the conditions to be treated. In general, an effective dose for compounds of Formula (I) or pharmaceutically acceptable salts thereof, is in the range of  
25           about 0.1 mg to about 3,500 mg per day. For a normal adult human having a body mass of about 70 kg, a dosage in the range of about 0.01 mg to about 50 mg per kg body mass is typically sufficient, and preferably about 0.2 to 2.5 mg per kg, in single or divided doses daily. Administration may be in single (e.g. once daily) or multiple doses or via constant infusion.

30           Some variability in the general dosage range may be required depending upon the age and mass of the subject being treated, the intended

route of administration, the particular compound being administered, and the like. The determination of dosage ranges and optimal dosages for a particular mammalian subject is within the ability of a skilled person having benefit of the instant disclosure.

5           The compounds of Formula (I) may be administered by a variety of conventional routes of administration, including oral, buccal, sublingual, ocular, topical (e.g. transdermal), parenteral (e.g. intravenous, intramuscular, or subcutaneous), rectal, intracisternal, intravaginal, intraperitoneal, intravesical, local (e.g. powder, ointment, or drop), nasal and/or inhalation  
10 dosage forms or using a "flash" formulation, *i.e.*, allowing the medication to dissolve in the mouth without the need to use water. As will be recognized by one of skill in the art, the appropriate dosage regimen, the amount of each dose administered and the intervals between doses of the compound will depend upon the compound of Formula (I), or the prodrug thereof, being  
15 used, the type of pharmaceutical compositions being used, the characteristics of the subject being treated, and/or the severity of the conditions being treated.

Methods of preparing various pharmaceutical compositions with amounts of active ingredients are known, or will be apparent in light of this  
20 disclosure, to those skilled in this art. See, for example, Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, 19th Ed. (1995).

Suitable pharmaceutical carriers, vehicles and diluents for such compositions include inert solid diluents or fillers, sterile aqueous solutions and various organic solvents. The pharmaceutical compositions formed by  
25 combining a compound of this invention and pharmaceutically acceptable carriers, vehicles or diluents are readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like.

Solid dosage forms for oral administration include capsules, tablets,  
30 powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert conventional pharmaceutical excipient (or

carrier) such as sodium citrate, calcium carbonate, or dicalcium phosphate, or (a) fillers or extenders, such as for example, starches, lactose, sucrose, mannitol and silicic acid; (b) binders, such as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; (c) humectants, such as for example, glycerol; (d) disintegrating agents, such as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (e) solution retarders, such as for example, paraffin; (f) absorption accelerators, such as for example, quaternary ammonium compounds; (g) wetting agents, such as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, such as for example, kaolin and bentonite; and/or (i) lubricants, such as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate or mixtures thereof. In the case of capsules and tablets, the dosage forms may further comprise buffering agents.

15 Solid dosage forms may be formulated as modified release and pulsatile release dosage forms containing excipients such as those detailed above for immediate release dosage forms together with additional excipients that act as release rate modifiers, these being coated on and/or included in the body of the device. Release rate modifiers include, but are not limited to, hydroxypropylmethyl cellulose, methyl cellulose, sodium carboxymethylcellulose, ethyl cellulose, cellulose acetate, polyethylene oxide, xanthan gum, ammoniomethacrylate copolymer, hydrogenated castor oil, carnauba wax, paraffin wax, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, methacrylic acid copolymer and mixtures thereof.

20

25 Modified release and pulsatile release dosage forms may contain one or a combination of release rate modifying excipients.

The pharmaceutical compositions of the invention may further comprise fast dispersing or dissolving dosage formulations (FDDFs). The terms dispersing or dissolving as used herein to describe FDDFs are dependent upon the solubility of the drug substance used i.e., where the drug substance is insoluble, a fast dispersing dosage form may be prepared, and

30

where the drug substance is soluble, a fast dissolving dosage form may be prepared.

Solid compositions of a similar type may also be employed as fillers in soft or hard filled gelatin capsules using such excipients as lactose or milk sugar, as well as high molecular weight polyethylene glycols and the like.

Solid dosage forms such as tablets, dragees, capsules, and granules can be prepared with coatings and shells, such as enteric coatings and others well-known to one of ordinary skill in the art. They may also comprise opacifying agents, and can also be of such composition that they release the active compound(s) in a delayed, sustained or controlled manner. Examples of embedding compositions that can be employed are polymeric substances and waxes. The active compound(s) can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage form may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethanol, isopropanol, ethyl carbonate, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame seed oil), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances, and the like.

In addition to the active compound(s), the pharmaceutical composition may further include suspending agents, such as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, or mixtures of these substances, and the like. Sweeteners, flavoring, and perfuming agents may also be included.

The pharmaceutical compositions of the invention may further comprise adjuvants, such as preserving, wetting, emulsifying and dispersing agents. Prevention of microorganism contamination of the instant compositions can be

accomplished with various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride and the like. Prolonged absorption of injectable pharmaceutical compositions may  
5 be affected by the use of agents capable of delaying absorption, for example, aluminum monostearate and gelatin.

For parenteral administration, solutions in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solutions may be employed. Such aqueous solutions should be suitably buffered if necessary and the  
10 liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, the sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

15 For intranasal administration or administration by inhalation, the compounds of Formula (I) are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., carbon dioxide  
20 dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of a compound of this invention. Capsules and cartridges (made, for example,  
25 from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound or compounds of the invention and a suitable powder base such as lactose or starch.

Pharmaceutical compositions of the present invention may also be configured for treatments in veterinary use, where a compound of the present  
30 invention, or a veterinarily acceptable salt thereof, or veterinarily acceptable solvate or pro-drug thereof, is administered as a suitably acceptable



formulation in accordance with normal veterinary practice and the veterinary practitioner will determine the dosing regimen and route of administration which will be most appropriate for a particular animal.

In general, the compounds of Formula (I), and pharmaceutically acceptable salts thereof, may be prepared according to the exemplary routes disclosed in the Schemes and Examples below, as well as by other conventional preparative procedures known, or apparent in light of the instant disclosure, to one of ordinary skill in the art. These processes form further aspects of the invention.

Some of the starting compounds for the reactions described in the Schemes and Examples are prepared as illustrated herein. All other starting compounds may be obtained from general commercial sources, such as Sigma-Aldrich Corp., St. Louis, MO.

Unless indicated otherwise, the following experimental abbreviations have the meanings indicated in Table 1:

|  |                                       |
|--|---------------------------------------|
| $\mu\text{L}$ – microliter                   | m – multiplet                         |
| br d – broad doublet                         | MHz – megahertz                       |
| br m – broad multiplet                       | min(s) – minute(s)                    |
| BOC – <i>t</i> -butoxycarbonyl               | MeOH – methanol                       |
| br s – broad singlet                         | mg – milligram                        |
| $\text{CDCl}_3$ – deuterated chloroform      | mL – milliliter                       |
| $\text{CD}_3\text{OD}$ – deuterated methanol | mmol – millimoles                     |
| dd – doublet of doublets                     | MS – mass spectroscopy                |
| DMF – dimethylformamide                      | mw – molecular weight                 |
| DMSO – dimethyl sulfoxide                    | NMR – nuclear magnetic resonance      |
| dt – doublet of triplets                     | PMSF – phenylmethanesulfonyl fluoride |
| EtOAc – ethyl acetate                        | ppm – parts per million               |
| EtOH – ethanol                               | psi – pounds per square inch          |
| h (e.g., 1h, 2h) – hour(s)                   | s – singlet                           |

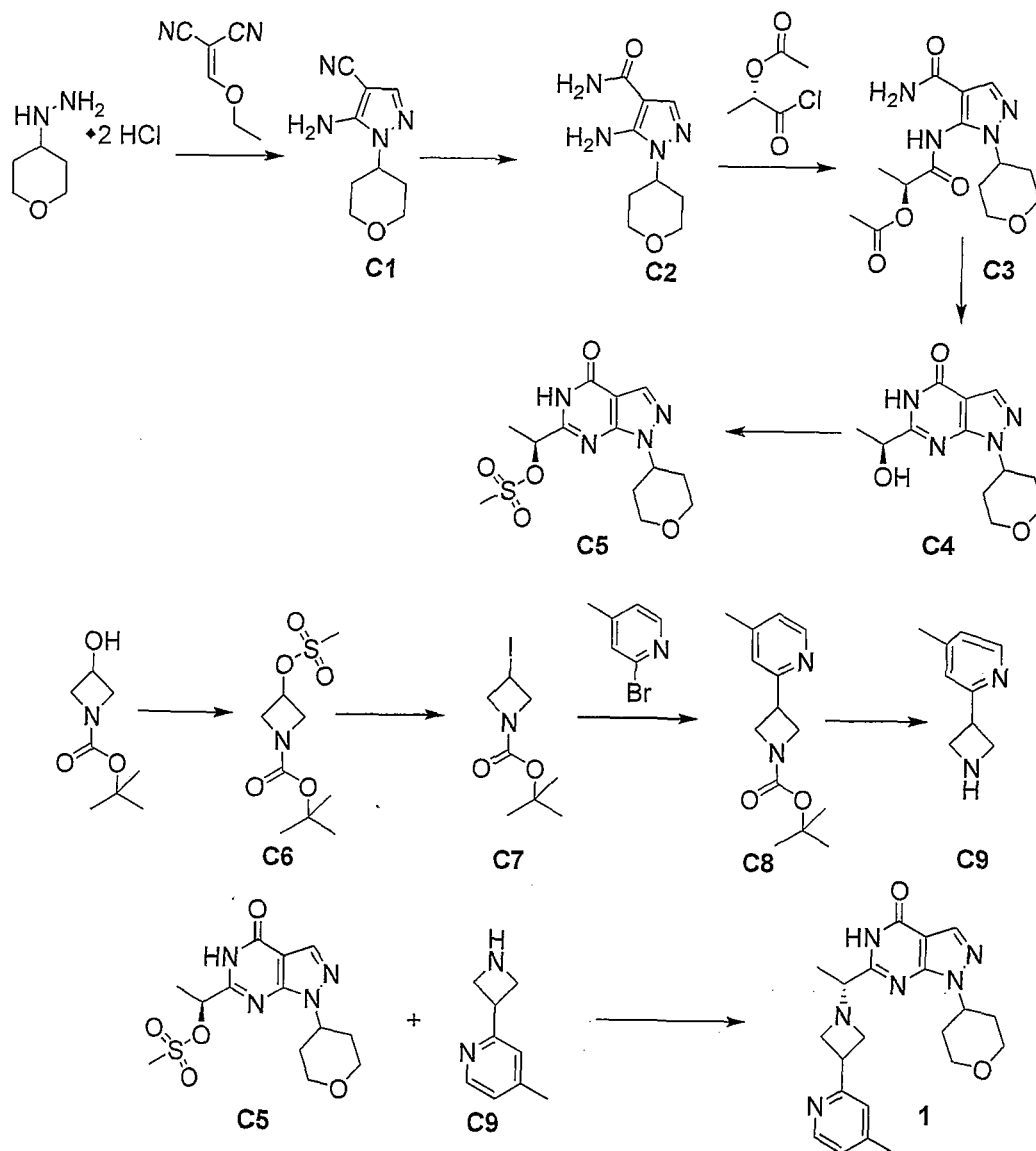
|                                 |   |
|---------------------------------|---|
| H (e.g., 1H, 2H) – hydrogen(s)  | SPA – scintillation proximity assay       |
| Hz – hertz                      | t – triplet                               |
| IPA – isopropyl alcohol         | temp – temperature                        |
| J – spin-spin coupling constant | THF – tetrahydrofuran                     |
| LC – liquid chromatography      | Tris –<br>tris(hydroxymethyl)aminomethane |

The methods disclosed in the instant Schemes and Examples are intended for purposes of exemplifying the instant invention only and are not to be construed as limitations thereon.

## 5 Experimental Procedures

Experiments were generally carried out under inert atmosphere (nitrogen or argon), particularly in cases where oxygen- or moisture-sensitive reagents or intermediates were employed. Commercial solvents and reagents were generally used without further purification, including anhydrous solvents where appropriate (generally Sure-Seal™ products from the Aldrich Chemical Co., Milwaukee, WI). Mass spectrometry data is reported from either liquid chromatography-mass spectrometry (LCMS) or atmospheric pressure chemical ionization (APCI) instrumentation. Chemical shifts for nuclear magnetic resonance (NMR) data are expressed in parts per million (ppm,  $\delta$ ) referenced to residual peaks from the deuterated solvents employed, or to tetramethylsilane standard.

## Example 1

6-{(1*R*)-1-[3-(4-Methylpyridin-2-yl)azetidin-1-yl]ethyl}-1-(tetrahydro-2*H*-pyran-4-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one

5 Step 1. Preparation of (1*S*)-1-[4-oxo-1-(tetrahydro-2*H*-pyran-4-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl]ethyl methanesulfonate (**C5**).

A. Preparation of 5-amino-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazole-4-carbonitrile (**C1**). To a solution of tetrahydro-2*H*-pyran-4-ylhydrazine dihydrochloride (See R.R. Ranatunge *et al.*, *J. Med. Chem.* 2004, 47, 2180-  
 10 2193) (43 g, 228 mmol) in EtOH (300 mL) was slowly added sodium ethoxide (32.6 g, 479 mmol), and the resulting mixture was stirred at room temp for 1 h. The reaction mixture was then transferred into a solution of

(ethoxymethylene)malononitrile (27.8 g, 228 mmol) in EtOH (300 mL). After being stirred at room temp for 30 mins, the reaction was heated at reflux for 2 h. It was then cooled to room temp and concentrated *in vacuo* to afford **C1** as an orange solid, which was used in the next step without purification.

5        B. Preparation of 5-amino-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazole-4-carboxamide (**C2**). A solution of **C1** ( $\leq$  228 mmol) in EtOH (300 mL) was treated with 35% aqueous hydrogen peroxide (100 mL) followed by concentrated aqueous ammonia solution (300 mL). The reaction mixture was stirred for 48 h at room temp, then quenched with saturated aqueous sodium  
10    thiosulfate solution (800 mL). Removal of most of the EtOH *in vacuo* provided a solid that was isolated by filtration and washed with water (2 x 200 mL) and diethyl ether (2 x 150 mL) to provide **C2** as a solid. Yield: 31 g, 147 mmol, 64% for 2 steps. MS (APCI)  $m/z$  211.2 (M+1).  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  1.70 (m, 2H), 1.93 (m, 2H), 3.40 (m, 2H), 3.95 (dd,  $J=11.1, 3.2$  Hz, 2H), 4.26  
15    (m, 1H), 6.24 (m, 2H), 6.67 (br s, 1H), 7.20 (br s, 1H), 7.66 (s, 1H).

C. Preparation of (1S)-2-[[4-carbamoyl-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-5-yl]amino]-1-methyl-2-oxoethyl acetate (**C3**). (1S)-2-Chloro-1-methyl-2-oxoethyl acetate (30 g, 199 mmol) was added to a suspension of **C2** (38.1 g, 181 mmol) in dry dioxane (1000 mL). The mixture was heated at  
20    reflux for 2 h, then concentrated *in vacuo* to provide **C3**, which was used in the next step without purification.

D. Preparation of 6-[(1S)-1-hydroxyethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4- $d$ ]pyrimidin-4-one (**C4**). A suspension of **C3** ( $\leq$ 181 mmol) in water (700 mL) was treated with anhydrous potassium  
25    carbonate (100 g). The mixture was heated at 45°C for about 18 h, then neutralized with acetic acid and extracted with chloroform (4 x 1 L). The combined organic layers were washed with saturated aqueous sodium chloride solution and dried over sodium sulfate. Filtration and removal of solvents *in vacuo* provided **C4** as an off-white solid. Yield: 43.1 g, 163 mmol,  
30    90% over 2 steps. LCMS  $m/z$  265.2 (M+1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.67 (d,  $J=6.6$  Hz, 3H), 1.92 (br d,  $J=13$  Hz, 2H), 2.39 (m, 2H), 3.62 (br dd,

apparent br t,  $J=12$ , 12 Hz, 2H), 4.15 (br dd,  $J=11.7$ , 4 Hz, 2H), 4.84 (tt,  $J=11.6$ , 4.3 Hz, 1H), 4.90 (q,  $J=6.7$  Hz, 1H), 8.08 (s, 1H), 10.65 (br s, 1H).

E. Preparation of compound **C5**. A solution of **C4** (20.0 g, 75.7 mmol) in dichloromethane (400 mL) was treated with triethylamine (15.8 mL, 113 mmol), cooled to 0°C and stirred for 30 mins. Methanesulfonyl chloride (99%, 5.92 mL, 75.7 mmol) was added drop-wise to the cold reaction, which was allowed to warm to room temp over the next 18 h. Solvents were removed *in vacuo*, and the residue was purified by silica gel chromatography (Gradient: 0% to 5% MeOH in dichloromethane). Rechromatography of mixed fractions provided additional product, to afford **C5** as a solid. Total yield: 10.6 g, 31.0 mmol, 41%. LCMS  $m/z$  341.1 (M-1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.86 (d,  $J=6.6$  Hz, 3H), 1.93 (br d,  $J=12$  Hz, 2H), 2.39 (m, 2H), 3.23 (s, 3H), 3.61 (ddd, apparent td,  $J=12$ , 12, 2.1 Hz, 2H), 4.16 (br dd,  $J=11.4$ , 3.5 Hz, 2H), 4.86 (tt,  $J=11.7$ , 4.2 Hz, 1H), 5.70 (q,  $J=6.7$  Hz, 1H), 8.08 (s, 1H).

15 Step 2. Preparation of 2-azetidin-3-yl-4-methylpyridine (**C9**).

A. Preparation of *tert*-butyl 3-[(methylsulfonyl)oxy]azetidine-1-carboxylate (**C6**). A solution of *tert*-butyl 3-hydroxyazetidine-1-carboxylate (97%, 5.0 g, 28 mmol) in dichloromethane (50 mL) was treated with triethylamine (7.8 mL, 56 mmol) and cooled to 0°C. A solution of methanesulfonyl chloride (2.28 mL, 29.3 mmol) in dichloromethane was added drop-wise to the cold reaction, which was maintained at 0°C for 2 h, then allowed to warm to room temp over the next 18 h. Solvents were removed *in vacuo* and the residue was taken up in ether and filtered. The filtrate was concentrated *in vacuo*, and the residue purified via silica gel chromatography (Eluant: 5:1 heptane: EtOAc, then 2:1 heptane: EtOAc) to provide **C6** as a solid. Yield: 6.5 g, 26.0 mmol, 93%. LCMS  $m/z$  503.1 (2M+1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.44 (s, 9H), 3.06 (s, 3H), 4.09 (ddd,  $J=10.4$ , 4.2, 1.2, 2H), 4.27 (ddd,  $J=10.4$ , 6.6, 1.2 Hz, 2H), 5.19 (tt,  $J=6.6$ , 4.2 Hz, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  28.23, 38.33, 56.45 (br), 67.25, 80.29, 155.80.

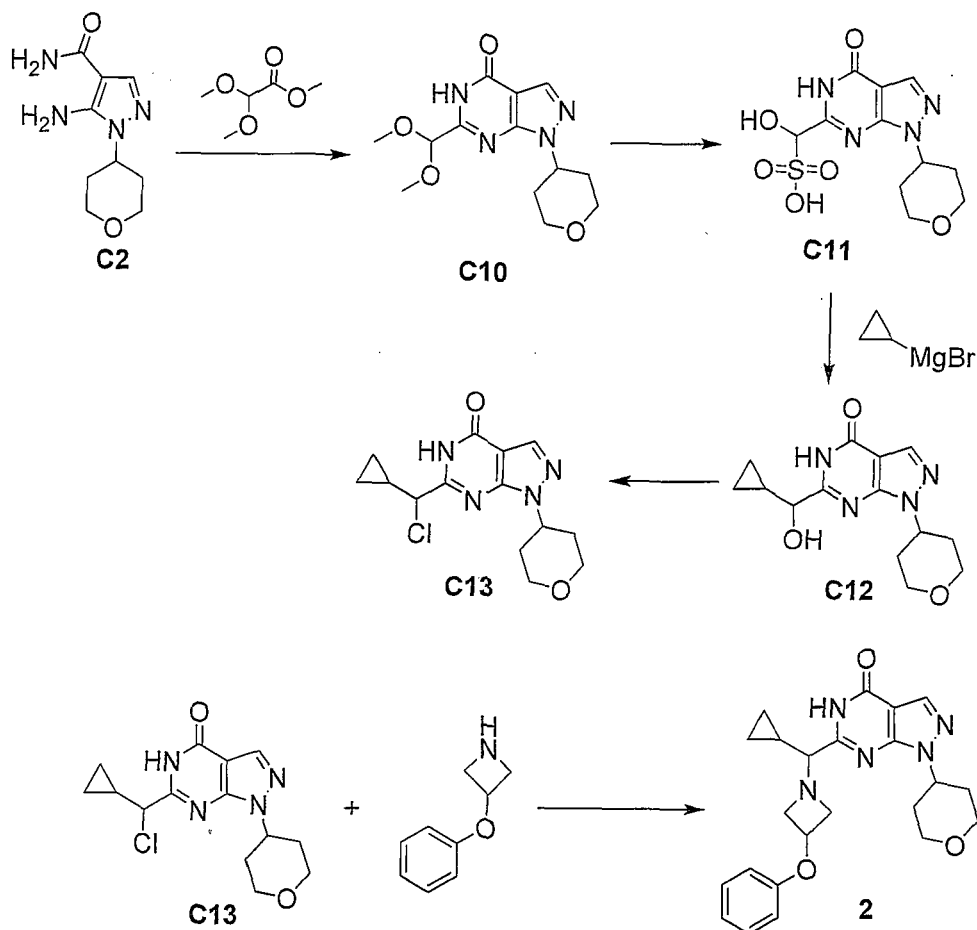
B. Preparation of *tert*-butyl 3-iodoazetidine-1-carboxylate (**C7**). Potassium iodide (12.9 g, 77.7 mmol) and **C6** (6.5 g, 26.0 mmol) were combined in DMF (40 mL). The reaction mixture was stirred at 110°C for 16 h, then concentrated *in vacuo*, diluted with water, and extracted with EtOAc. 5 The combined organic layers were washed with water, then washed with saturated aqueous sodium chloride solution and dried over magnesium sulfate. Filtration and removal of solvent *in vacuo* gave a residue, which was purified by silica gel chromatography (Eluant: 4:1 heptane: EtOAc) to afford **C7** as a solid. Yield: 6.2 g, 21.9 mmol, 84%. LCMS *m/z* 284.0 (M+1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.43 (s, 9H), 4.28 (m, 2H), 4.46 (m, 1H), 4.64 (m, 10 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 2.57, 28.27, 61.49, 80.09, 155.52.

C. Preparation of *tert*-butyl 3-(4-methylpyridin-2-yl)azetidine-1-carboxylate (**C8**). 1,2-Dibromoethane (98%, 0.031 mL, 0.35 mmol) was added to a suspension of zinc dust (98%, 354 mg, 5.3 mmol) in THF (15 mL), 15 and the reaction mixture was heated to reflux for 1 h. After cooling to room temp, the reaction mixture was treated with trimethylsilyl chloride (99%, 0.045 mL, 0.35 mmol) and stirred for 1 h. At this point, a solution of **C7** (1.0 g, 3.53 mmol) in THF (5 mL) was added drop-wise. The reaction was stirred for 1 h at 60°C and cooled to room temp. 2-Bromo-4-methylpyridine (97%, 0.486 mL, 20 4.2 mmol) and tetrakis(triphenylphosphine)palladium(0) (99%, 82.9 mg, 0.071 mmol) were added, and the mixture was heated at reflux for 1 h, then stirred at room temp for about 18 h. The reaction was filtered through Celite (diatomaceous earth), and the filtrate was concentrated, then treated with EtOAc and saturated aqueous sodium carbonate solution. The resulting 25 precipitate was removed by filtration and the filter cake was washed with EtOAc. The combined filtrates were washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by silica gel chromatography (Gradient: 1:4 to 1:1 EtOAc: heptane) provided **C8** as a solid. Yield: 245 mg, 0.987 mmol, 28%. LCMS 30 *m/z* 249.2 (M+1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.44 (s, 9H), 2.33 (s, 3H), 3.82 (tt, *J*=8.9, 6.0 Hz, 1H), 4.13 (m, 2H), 4.28 (dd, apparent t, *J*=8.7, 8.7 Hz, 2H),

6.98 (d,  $J=5.0$  Hz, 1H), 7.05 (s, 1H), 8.43 (d,  $J=5.0$  Hz, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.96, 28.36, 34.90, 54.6 (v br), 79.30, 122.46, 122.88, 147.67, 149.30, 156.38, 160.64.

D. Preparation of compound **C9**. Compound **C8** (124 mg, 0.50 mmol) was mixed with dichloromethane (2 mL) and treated with trifluoroacetic acid (1 mL). The reaction mixture was stirred at room temp for about 18 h, then concentrated *in vacuo* to afford compound **C9**, which was used in the next step without purification, assuming quantitative conversion. LCMS  $m/z$  149.1 ( $M+1$ ).

10 Step 3. Synthesis of title compound **1**. Compound **C5** (114 mg, 0.333 mmol) and compound **C9** (74.1 mg, 0.50 mmol) were combined in acetonitrile (2 mL) and toluene (2 mL), and treated with triethylamine (0.116 mL, 0.83 mmol). The reaction mixture was heated to 90°C for 5 h, then cooled and concentrated *in vacuo*. The residue was purified via silica gel  
15 chromatography (Eluant: 100:1 chloroform: MeOH) to provide compound **1** as a solid. Yield: 92 mg, 0.23 mmol, 69%. LCMS  $m/z$  395.1 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.33 (d,  $J=6.8$  Hz, 3H), 1.91 (m, 2H), 2.34 (s, 3H), 2.37 (m, 2H), 3.44 (dd, apparent t,  $J=7, 7$  Hz, 1H), 3.60 (m, 4H), 3.77 (m, 3H), 4.14 (br d,  $J=11.6$  Hz, 2H), 4.83 (tt,  $J=11.6, 4.2$  Hz, 1H), 6.99 (d,  $J=5.0$  Hz, 1H),  
20 7.03 (s, 1H), 8.06 (s, 1H), 8.44 (d,  $J=5.0$  Hz, 1H).

Example 26-[Cyclopropyl(3-phenoxyazetidin-1-yl)methyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

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Step 1. Preparation of 6-[chloro(cyclopropyl)methyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (**C13**).

A. Preparation of 6-(dimethoxymethyl)-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (**C10**). Methyl dimethoxyacetate (19.9 g, 148 mmol) and compound **C2** (15.6 g, 74.2 mmol) were combined with molecular sieves (16 g), and the mixture was treated with a solution of potassium *t*-butoxide in THF (1.0M, 150 mL, 150 mmol). The reaction mixture was heated to reflux for about 18 h; it was then filtered, and the collected solid was rinsed with additional THF. The combined filtrates were neutralized with acetic acid and concentrated *in vacuo*. The residue was

15



purified by silica gel chromatography (Eluant: 5% MeOH in chloroform) to afford **C10** as a white solid. Yield: 9.8 g, 33 mmol, 44%. MS (APCI)  $m/z$  295.2 (M+1).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.91 (br d,  $J=10.5$  Hz, 2H), 2.38 (m, 2H), 3.48 (s, 6H), 3.60 (dd,  $J=11, 12$ , 2H), 4.14 (br d,  $J=11$  Hz, 2H), 4.90 (m, 1H), 5.22 (s, 1H), 8.10 (s, 1H), 9.52 (br s, 1H).

B. Preparation of hydroxy[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-*d*]pyrimidin-6-yl]methanesulfonic acid (**C11**). Compound **C10** (1.0 g, 3.4 mmol) was combined with aqueous hydrochloric acid (1N, 10 mL) and THF (10 mL), and treated with *para*-toluenesulfonic acid monohydrate (646 mg, 3.40 mmol). The reaction mixture was heated to 67°C for 16 h, during which time it became a light yellow solution. This was cooled to room temperature and adjusted to pH 7 with 1N aqueous sodium hydroxide. Sodium bisulfite (707 mg, 6.79 mmol) was added, and the reaction was allowed to stir for 1 h at room temp. Removal of solvents *in vacuo* was followed by three azeotropes with EtOH, to provide crude **C11** as an off-white solid, which still contained excess sodium bisulfite and an equivalent of *para*-toluenesulfonic acid, sodium salt. This crude material was used in the next reaction. Recovery: 2.9 g, assumed quantitative.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ), product peaks only:  $\delta$  1.84 (m, 2H), 2.11 (m, 2H), 3.54 (br dd, apparent t,  $J=12, 12$  Hz, 2H), 3.98 (br dd,  $J=11.3, 4$  Hz, 2H), 4.38 (br s, 1H), 4.88 (m, 1H), 4.93 (br s, 1H), 6.78 (br s, 1H), 8.08 (s, 1H).

C. Preparation of 6-[cyclopropyl(hydroxy)methyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-*d*]pyrimidin-4-one (**C12**). Crude **C11** (1.45 g,  $\leq 1.7$  mmol) from the previous step was slurried in THF (10 mL) and treated portion-wise with a solution of cyclopropylmagnesium bromide in THF (0.50M, 33.9 mL, 17 mmol). A slight exotherm was observed, and the reaction became yellow; it was heated to reflux for 16 h, then cooled to room temperature and quenched with an aqueous solution of ammonium chloride (3M, 20 mL) {*Caution*: exothermic and gas evolution}. The mixture was allowed to stir for 1 h at room temp, then extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and

concentrated *in vacuo*. The resulting residue was purified via silica gel chromatography (Gradient: dichloromethane to 2.5% MeOH in dichloromethane) to provide **C12** as a light yellow solid/gum, contaminated with extraneous cyclopropyl material, as assessed by  $^1\text{H}$  NMR. This material  
5 was taken on to the next step. Yield: 252 mg, <0.87 mmol, <51%. LCMS  $m/z$  289.3 ( $M-1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ), product peaks only:  $\delta$  0.56 (m, 4H), 1.24 (m, 1H), 1.90 (m, 2H), 2.36 (dddd,  $J=12, 12, 12, 4.6$  Hz, 2H), 3.58 (dd,  $J=12, 12$  Hz, 2H), 4.12 (br dd,  $J=11.7, 4$  Hz, 2H), 4.17 (d,  $J=7.0$  Hz, 1H), 4.81 (tt,  $J=11.6, 4.2$  Hz, 1H), 8.04 (s, 1H).

10 D. Preparation of compound **C13**. A solution of **C12** (252 mg, <0.87 mmol) in dichloromethane (5 mL) was treated with triethylamine (0.18 mL, 1.3 mmol) and methanesulfonyl chloride (0.08 mL, 1.0 mmol) and allowed to stir at room temperature for 16 h. The reaction was then poured into water and the mixture was extracted with dichloromethane. The combined organic  
15 layers were washed twice with water, once with 1N aqueous hydrochloric acid and once with saturated aqueous sodium bicarbonate solution, then dried over magnesium sulfate. Filtration and removal of solvent under reduced pressure provided a residue that was purified by silica gel chromatography (Gradient: dichloromethane to 1.5% MeOH in dichloromethane), to provide  
20 **C13** as a light yellow gum. Yield: 100 mg, 0.32 mmol, 19% over three steps. LCMS  $m/z$  309.3 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.68 (m, 2H), 0.79 (m, 1H), 0.93 (m, 1H), 1.74 (m, 1H), 1.95 (m, 2H), 2.40 (m, 2H), 3.62 (br dd,  $J=12, 12$  Hz, 2H), 4.16 (br d,  $J=12$  Hz, 2H), 4.21 (d,  $J=9.5$  Hz, 1H), 4.86 (tt,  $J=11.7, 4.2$  Hz, 1H), 8.12 (s, 1H), 11.00 (br s, 1H).

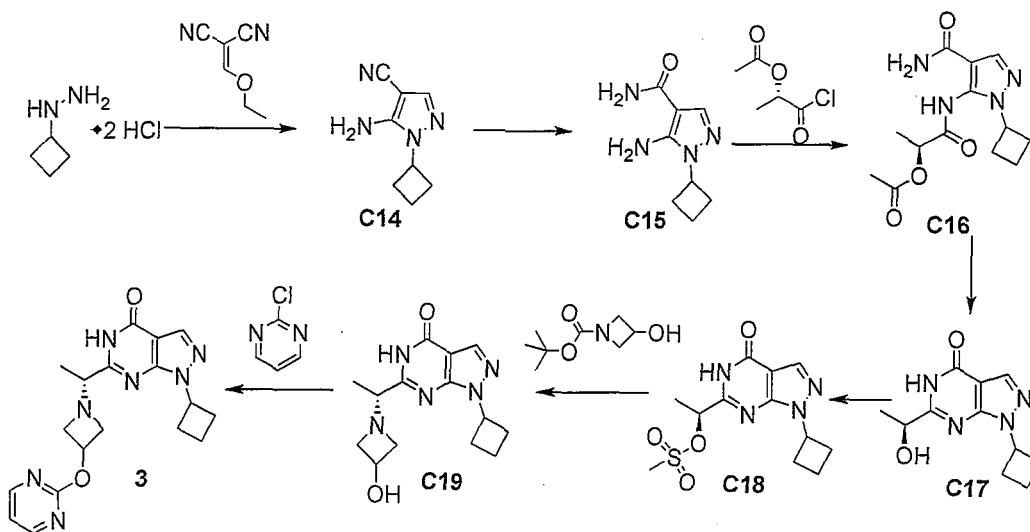
25 Step 2. Synthesis of title compound **2**. Compound **C13** (100 mg, 0.32 mmol), 3-phenoxyazetidine (75.6 mg, 0.407 mmol) and triethylamine (0.102 mL, 0.732 mmol) were combined in acetonitrile (3 mL) and heated to reflux for 16 h. The reaction mixture was cooled to room temperature and poured into water. The resulting mixture was extracted twice with dichloromethane, and  
30 the organic layers were washed with water, then with saturated aqueous sodium bicarbonate solution. The organic layers were dried over magnesium

sulfate, filtered and concentrated *in vacuo*; purification via silica gel chromatography (Eluant 2.5% MeOH in dichloromethane) afforded compound 2. Yield: 27 mg, 0.064 mmol, 20%. LCMS  $m/z$  422.3 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.46 (m, 2H), 0.58 (m, 1H), 0.77 (m, 1H), 0.86 (m, 1H), 1.93 (m, 2H), 2.39 (m, 2H), 2.63 (d,  $J=8.9$  Hz, 1H), 3.19 (dd,  $J=7.6, 6.1$  Hz, 1H), 3.52 (dd,  $J=7.9, 6.0$  Hz, 1H), 3.61 (m, 2H), 3.83 (br dd,  $J=7, 7$  Hz, 1H), 4.01 (br dd,  $J=7, 7$  Hz, 1H), 4.15 (br dd,  $J=11.4, 4$  Hz, 2H), 4.82 (tt,  $J=11.8, 4.2$  Hz, 1H), 4.85 (m, 1H), 6.78 (br d,  $J=8.6$  Hz, 2H), 6.98 (br t,  $J=7.4$  Hz, 1H), 7.29 (dd,  $J=8.8, 7.4$  Hz, 2H), 8.07 (s, 1H), 9.74 (br s, 1H).

10

Example 3

1-Cyclobutyl-6-[(1R)-1-[3-(pyrimidin-2-yloxy)azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Step 1. Preparation of 5-amino-1-cyclobutyl-1H-pyrazole-4-carbonitrile (**C14**).

15 A suspension of cyclobutylhydrazine dihydrochloride (11.63 g, 73.12 mmol) in EtOH (110 mL) was cooled in an ice bath and treated portion-wise with solid sodium ethoxide (9.95 g, 146 mmol) over 45 mins, while keeping the internal temp of the reaction mixture at approximately 0°C. The mixture was stirred in the ice bath for an additional hour, and then a solution of (ethoxymethylene)malononitrile (8.93 g, 73.1 mmol) in EtOH (70 mL) was added drop-wise over about 1.5 h, at a rate which maintained the internal temperature of the reaction mixture between 0°C and 5°C. The reaction was

then allowed to warm to room temp over about 18 h, after which it was heated at reflux for 1.5 h. After cooling to room temp, solvents were removed *in vacuo*, and the residue was partitioned between EtOAc and water. The aqueous layer was extracted twice with additional EtOAc, and the combined  
5 organic layers were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to provide crude **C14**, which was used in the next step without purification. Yield: 14.1 g, >100% mass recovery. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.9 (m, 2H), 2.4 (m, 2H), 2.65 (m, 2H), 4.25 (br s, 2H), 4.45 (m, 1H),  
10 7.5 (s, 1H).

Step 2. Preparation of 5-amino-1-cyclobutyl-1H-pyrazole-4-carboxamide (**C15**). Crude **C14** (14.1 g, ≤ 73.12 mmol) was cooled in an ice bath and treated with pre-cooled (ice bath) concentrated sulfuric acid (55 mL). The cooling bath was removed, and the reaction mixture agitated until a solution  
15 was obtained. After stirring at room temp for about 18 h, the reaction mixture was poured onto ice, which was itself cooled in an ice bath, and subsequently adjusted to a pH of about 11-12 by the addition of concentrated aqueous ammonium hydroxide. The resulting precipitate was collected by filtration and washed three times with water, then three times with diethyl ether, to provide  
20 **C15** as a yellow solid. Yield: 6.0 g, 33 mmol, 45% over two steps. MS (APCI) *m/z* 181.2 (M+1). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.73 (m, 2H), 2.27 (m, 2H), 2.44 (m, 2H), 4.68 (m, 1H), 6.15 (m, 2H), 6.6 (br s, 1H), 7.2 (br s, 1H), 7.68 (s, 1H).

Step 3. Preparation of (1S)-2-[(4-carbamoyl-1-cyclobutyl-1H-pyrazol-5-yl)amino]-1-methyl-2-oxoethyl acetate (**C16**). (1S)-2-Chloro-1-methyl-2-oxoethyl acetate (3.86 mL, 30.5 mmol) was slowly added to an ice-cooled suspension of **C15** (5.00 g, 27.7 mmol) in dry dioxane (120 mL). The mixture was heated at 111°C for 8 h, then cooled and stirred at room temp for about 18 h. The reaction was concentrated *in vacuo* to provide **C16**, which was  
30 used in the next step without purification.

Step 4. Preparation of 1-cyclobutyl-6-[(1S)-1-hydroxyethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (**C17**). Compound **C17** was prepared according to the general procedure for the synthesis of **C4** in Example 1, except that **C16** was used in place of **C3**. Additionally, in this case the crude product was purified via silica gel chromatography (Eluant: 50:1 chloroform: MeOH), to afford **C17** as a solid. Yield 5.70 g, 24.3 mmol, 87%. LCMS *m/z* 235.3 (M+1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.64 (d, *J*=6.6 Hz, 3H), 1.91 (m, 2H), 2.44 (m, 2H), 2.75 (m, 2H), 4.26 (br s, 1H), 4.89 (q, *J*=6.6 Hz, 1H), 5.25 (m, 1H), 8.06 (s, 1H), 11.07 (br s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 14.93, 22.42, 29.84, 50.92, 67.67, 104.42, 134.66, 151.71, 159.25, 161.48.

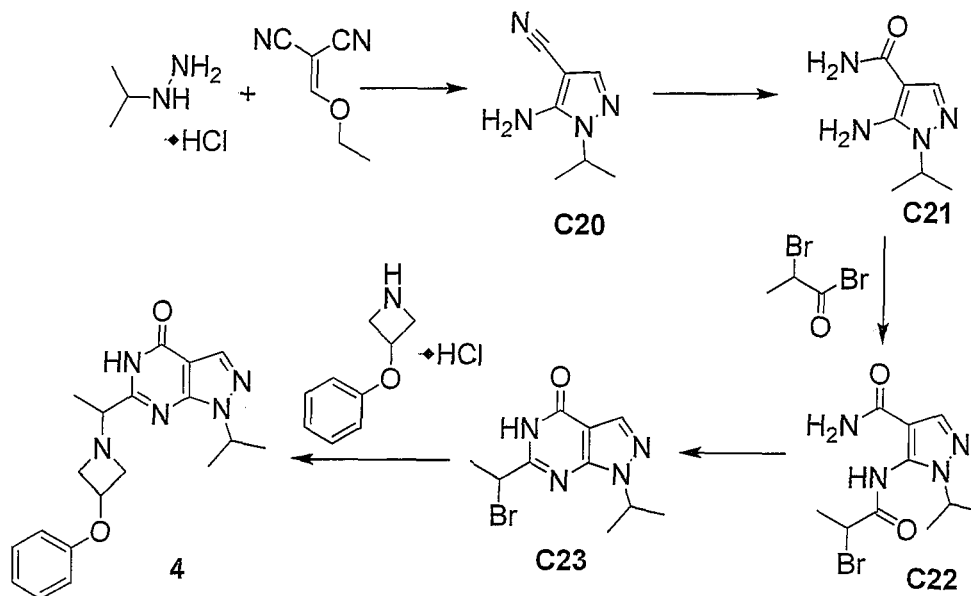
Step 5. Preparation of (1S)-1-(1-cyclobutyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)ethyl methanesulfonate (**C18**). Compound **C18** was prepared according to the general procedure for the synthesis of **C5** in Example 1, except that **C17** was used in place of **C4**, and the chromatographic purification was carried out with 0.5% to 1% MeOH in chloroform, rather than 0% to 5% MeOH in dichloromethane, to provide **C18** as a solid. Yield: 6.0 g, 19.2 mmol, 79%. LCMS *m/z* 311.4 (M-1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.85 (d, *J*=6.6 Hz, 3H), 1.93 (m, 2H), 2.46 (m, 2H), 2.78 (m, 2H), 3.23 (s, 3H), 5.29 (m, 1H), 5.69 (q, *J*=6.6 Hz, 1H), 8.08 (s, 1H), 11.65 (br s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 14.93, 20.39, 29.84, 38.75, 51.07, 74.91, 104.98, 134.71, 151.07, 155.61, 159.27.

Step 6. Preparation of 1-cyclobutyl-6-[(1R)-1-(3-hydroxyazetidin-1-yl)ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (**C19**). *tert*-Butyl 3-hydroxyazetidine-1-carboxylate (2.50 g, 14.4 mmol) was dissolved in dichloromethane (20 mL) and treated with trifluoroacetic acid (3.7 mL, 48 mmol); the reaction was allowed to stir at room temp for about 18 h. Solvents were removed *in vacuo*, and the residue was mixed with acetonitrile (20 mL) and toluene (20 mL). Finely ground potassium carbonate (13.3 g, 96 mmol) was then added, followed by compound **C18** (3.0 g, 9.6 mmol), and the mixture was heated to 90°C for 5 h. After cooling to room temp, the reaction was concentrated *in vacuo*, diluted with water and extracted with methylene

chloride. The combined organic layers were washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and concentrated. The resulting residue was purified via silica gel chromatography (Eluant: 2% MeOH in chloroform) to provide **C19** as a solid.

- 5 Yield: 1.95 g, 6.74 mmol, 70%. MS (APCI)  $m/z$  287.9 (M-1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.33 (d,  $J=6.8$  Hz, 3H), 1.90 (m, 2H), 2.44 (m, 2H), 2.76 (m, 2H), 3.17 (br dd,  $J=7$ , 4 Hz, 1H), 3.28 (br dd,  $J=7$ , 4 Hz, 1H), 3.58 (m, 3H), 4.44 (m, 1H), 5.28 (m, 1H), 8.12 (s, 1H).

- Step 7. Synthesis of title compound **3**. 2-Chloropyrimidine (79.2 mg, 0.691 mmol)), potassium *tert*-butoxide (163 mg, 1.45 mmol) and compound **C19** (200 mg, 0.691 mmol) were combined in THF (5 mL), and the mixture was heated at 70°C for 8 h. The reaction was cooled to room temp and concentrated *in vacuo*; the residue was partitioned between water and dichloromethane. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification via silica gel chromatography (Eluant: 0.5% to 1% MeOH in chloroform) provided **3** as a solid. Yield: 109 mg, 0.297 mmol, 43%. LCMS  $m/z$  368.4 (M+1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.38 (v br s, 3H), 1.91 (m, 2H), 2.45 (m, 2H), 2.76 (m, 2H), 3.32 (v br s, 1H), 3.53 (v br m, 2H), 3.97 (v br s, 2H), 5.28 (m, 2H), 6.99 (t,  $J=4.9$  Hz, 1H), 8.07 (s, 1H), 8.51 (d,  $J=5.0$  Hz, 2H)
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- 15
- 20

Example 41-Isopropyl-6-[1-(3-phenoxyazetidin-1-yl)ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

- 5 Step 1. Preparation of 5-amino-1-isopropyl-1H-pyrazole-4-carbonitrile (**C20**). (Ethoxymethylene)malononitrile (12.83 g, 105 mmol) and isopropylhydrazine hydrochloride (11.06 g, 100 mmol) were combined in EtOH (250 mL). Diisopropylethylamine (36.6 mL, 210 mmol) was added drop-wise, resulting in some warming of the reaction mixture. The reaction was allowed to stir for about 18 h at room temp. Volatiles were then removed *in vacuo*, and the resulting viscous yellow oil was dissolved in dichloromethane and loaded onto a short column of silica gel. The column was eluted with dichloromethane (about 300 mL), followed by a 1:1 mixture of EtOAc and hexanes (about 750 mL), and the EtOAc: hexanes eluant was concentrated under reduced pressure to provide **C20** as a pale yellow solid. Yield: 12.1 g, 80.6 mmol, 81%. LCMS *m/z* 151.1 (*M*+1). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.26 (d, *J*=6.6 Hz, 6H), 4.41 (septet, *J*=6.5 Hz, 1H), 6.52 (br s, 2H), 7.53 (s, 1H).
- 10 Step 2. Preparation of 5-amino-1-isopropyl-1H-pyrazole-4-carboxamide (**C21**). Compound **C20** (4.0 g, 27 mmol) was combined with concentrated sulfuric acid (about 10 mL) and stirred at room temp for 2 h. The reaction was then poured onto ice, adjusted to pH 9 with concentrated aqueous ammonium
- 15
- 20

hydroxide, and extracted with a mixture of dichloromethane and THF. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide **C21**. Yield: 3.02 g, 18.0 mmol, 67%. LCMS *m/z* 169.3 (*M*+1). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 1.39 (d, *J*=6.6 Hz, 6H), 4.39 (septet, *J*=6.6 Hz, 1H), 7.69 (s, 1H).

Step 3. Preparation of 5-[(2-bromopropanoyl)amino]-1-isopropyl-1*H*-pyrazole-4-carboxamide (**C22**). Compound **C21** (16.8 g, 100 mmol) was dissolved in a mixture of anhydrous DMF (400 mL) and triethylamine (30.8 mL, 221 mmol) and cooled to 0°C in an ice bath. 2-Bromopropanoyl bromide (43.2 g, 200 mmol) was added drop-wise, and the reaction was allowed to stir at 0°C for 30 mins, then at room temp for 2 h. The reaction mixture was then concentrated to about one-fifth the original volume, and partitioned between EtOAc (800 mL) and 2N aqueous hydrochloric acid (800 mL). The organic layer was washed with saturated aqueous sodium bicarbonate solution (800 mL), saturated aqueous sodium chloride solution (800 mL), and dried over sodium sulfate. Filtration and removal of solvent under reduced pressure provided **C22** as an orange residue, which was used in the next step without purification.

Step 4. Preparation of 6-(1-bromoethyl)-1-isopropyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (**C23**). *para*-Toluenesulfonic acid monohydrate (9.5 g, 50 mmol) was added to a suspension of crude **C22** (from the previous step, ≤100 mmol) in anhydrous toluene (800 mL), the flask was equipped with a Dean-Stark trap, and the mixture was heated at reflux for 16 h. The reaction was then cooled to room temperature and diluted with EtOAc. The resulting mixture was washed with aqueous sodium bicarbonate solution and then with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified via silica gel chromatography (Eluant: 100:1 chloroform: MeOH) to afford **C23** (contaminated with a second component) as a beige solid. Yield: 11.2 g, <39.3 mmol, <39% over two steps. LCMS *m/z* 285.4 (*M*+1). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) (major component only): δ 1.45 (d, *J*=6.7 Hz, 3H), 1.46 (d,

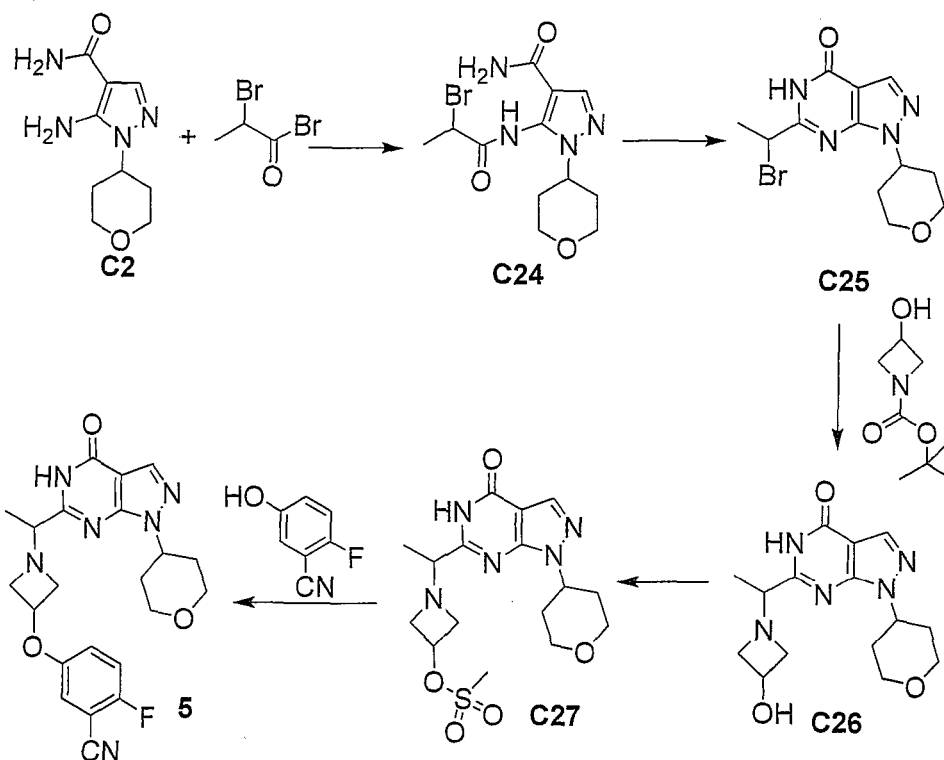


$J=6.7$  Hz, 3H), 1.99 (d,  $J=6.8$  Hz, 3H), 4.96 (septet,  $J=6.6$  Hz, 1H), 5.13 (q,  $J=6.8$  Hz, 1H), 8.06 (s, 1H), 12.36 (br s, 1H).

Step 5. Synthesis of title compound **4**. 3-Phenoxyazetidine hydrochloride (260 mg, 1.40 mmol), **C23** (200 mg, 0.701 mmol) and potassium carbonate (290 mg, 2.1 mmol) were combined in acetonitrile (10 mL). The reaction mixture was stirred at room temperature for 2 h, then at reflux for 3 h. The reaction was concentrated *in vacuo*, diluted with water, and extracted with dichloromethane. The combined organic layers were washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (Eluant: 200:1 chloroform: MeOH) to provide **4**. Yield: 149 mg, 0.42 mmol, 60%. MS (APCI)  $m/z$  354.0 (M+1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.35 (d,  $J=6.8$  Hz, 3H), 1.53 (d,  $J=6.6$  Hz, 6H), 3.22 (br dd,  $J=6, 7$  Hz, 1H), 3.39 (br dd,  $J=6.5, 6.5$  Hz, 1H), 3.55 (q,  $J=6.6$  Hz, 1H), 3.87 (m, 2H), 4.83 (m, 1H), 5.02 (septet,  $J=6.6$  Hz, 1H), 6.77 (d,  $J=7.7$  Hz, 2H), 6.97 (m, 1H), 7.28 (dd,  $J=8.5, 7.5$  Hz, 2H), 8.06 (s, 1H), 9.85 (br s, 1H).

## Example 5

2-Fluoro-5-[(1-{1-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]ethyl}azetidin-3-yl)oxy]benzonitrile



- 5 Step 1. Preparation of 5-[(2-bromopropanoyl)amino]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazole-4-carboxamide (**C24**). A solution of **C2** (5.0 g, 23.8 mmol) and triethylamine (3.65 mL, 26.2 mmol) in anhydrous DMF (50 mL) was cooled in an ice bath and treated drop-wise with 2-bromopropanoyl bromide (5.4 g, 25 mmol). The mixture was stirred at 0°C for 30 mins, warmed to room
- 10 temperature and stirred at ambient temperature for an additional 2 h. The reaction was partitioned between EtOAc (200 mL) and aqueous 2N hydrochloric acid (500 mL); the organic phase was washed with saturated aqueous sodium bicarbonate solution (400 mL), saturated aqueous sodium chloride solution (200 mL) and dried over sodium sulfate. Filtration and
- 15 concentration of the filtrate provided crude **C24** as an orange residue, which was used in the next step without purification.

Step 2. Preparation of 6-(1-bromoethyl)-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (**C25**). A suspension of **C24** from

the previous step ( $\leq 23.8$  mmol) in toluene (100 mL) was treated with *para*-toluenesulfonic acid (2.3 g, 11.9 mmol) and heated to reflux for 6 h using a Dean-Stark trap. The mixture was then cooled to room temp, diluted with EtOAc and washed with aqueous sodium bicarbonate solution followed by saturated aqueous sodium chloride solution. The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to provide a residue that was purified by silica gel chromatography (Eluant: 100:1 chloroform: MeOH). The resulting yellow-orange solid was subjected to a second silica gel column (Eluant 100:1 chloroform: MeOH) to provide **C25** as a yellow solid.

Yield: 1.1 g, 3.36 mmol, 14% over two steps. Purity: 85% by LCMS. LCMS  $m/z$  327.0, 329.1 for the two bromine isotopes ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  1.92 (m, 2H), 2.06 (d,  $J=6.3$  Hz, 3H), 2.31 (m, 2H), 3.63 (m, 2H), 4.08 (m, 2H), 4.94 (m, 1H), 5.09 (q,  $J=6.6$  Hz, 1H), 8.05 (s, 1H).

Step 3. Preparation of 6-[1-(3-hydroxyazetidin-1-yl)ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-*d*]pyrimidin-4-one (**C26**). A solution of *t*-butyl 3-hydroxyazetidine-1-carboxylate (519 mg, 3.00 mmol) in dichloromethane (10 mL) was treated with trifluoroacetic acid (0.77 mL, 10 mmol), and the resulting mixture was stirred at room temperature for about 18 h. Additional trifluoroacetic acid (0.5 mL) was added, and the reaction was stirred for an additional 3 h. Solvents were removed under reduced pressure, and acetonitrile (40 mL) was added to the residue, followed by solid potassium carbonate (2.76 g, 20 mmol), and **C25** (654 mg, 2.00 mmol). The mixture was stirred at room temp for 2 h, then heated to 90°C for 3 h. The reaction was cooled to room temp, diluted with dichloromethane and filtered; the remaining solid was washed with additional dichloromethane. The combined filtrates were concentrated *in vacuo*, then subjected to silica gel chromatography (Eluant: 40:1 to 20:1 chloroform: MeOH) to provide **C26**. Yield: 368 mg, 1.15 mmol, 58%. MS (APCI)  $m/z$  320.0 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.34 (d,  $J=6.8$  Hz, 3H), 1.91 (m, 2H), 2.38 (dddd, apparent qd,  $J=12, 12, 12, 4.6$  Hz, 2H), 3.17 (br s, 1H), 3.28 (br s, 1H), 3.52-3.68 (m, 5H),

4.14 (dd,  $J=11.3, 3.6$  Hz, 2H), 4.46 (m, 1H), 4.85 (tt,  $J=11.6, 4.2$  Hz, 1H), 8.10 (s, 1H).

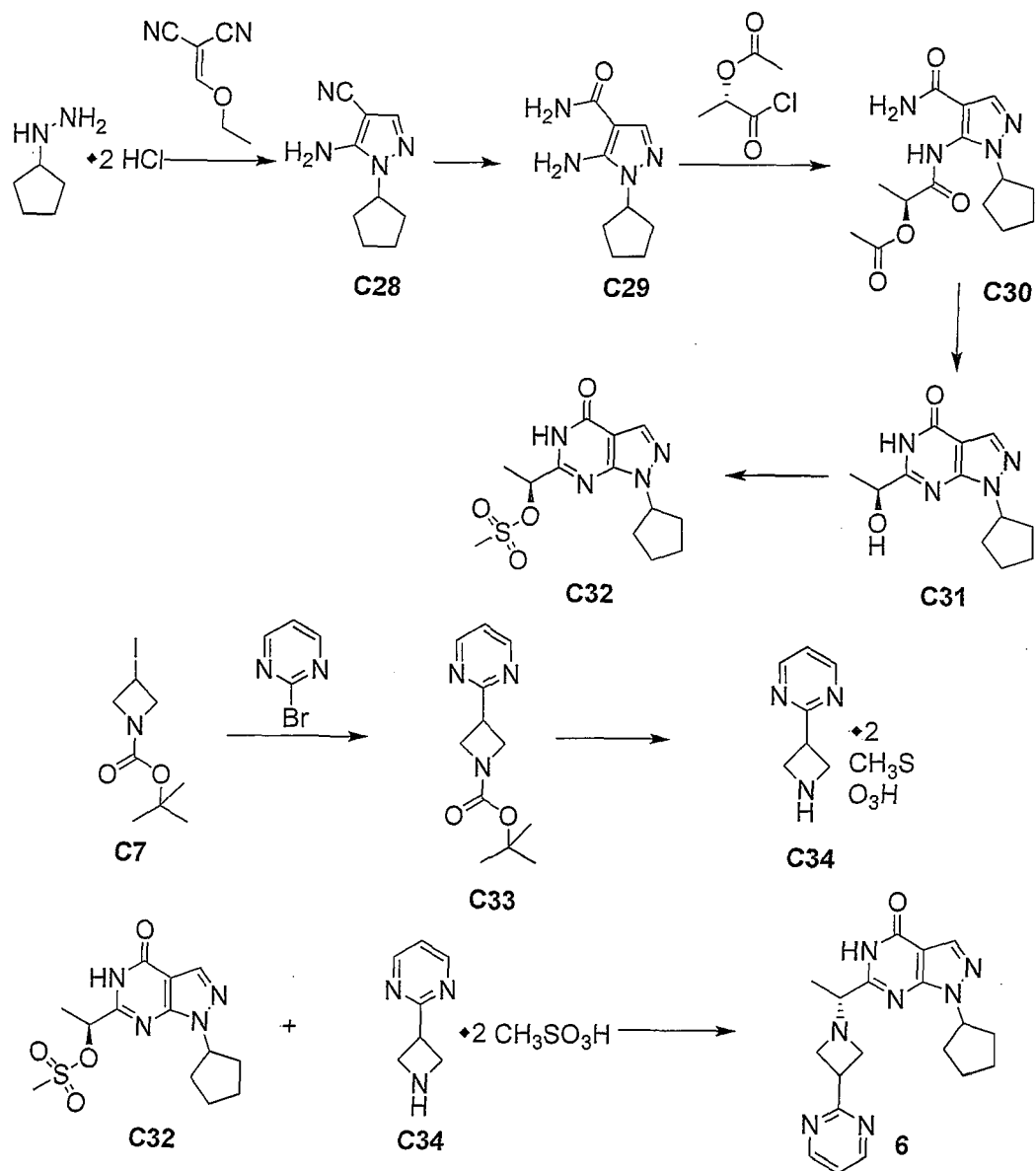
Step 4. Preparation of 1-{1-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]ethyl}azetidin-3-yl methanesulfonate (**C27**).

- 5 A solution of **C26** (1.34 g, 4.20 mmol) in dichloromethane (30 mL) was treated with triethylamine (1.17 mL, 8.41 mmol) and then drop-wise with methanesulfonyl chloride (0.49 mL, 6.3 mmol). The reaction was allowed to stir at room temperature for about 18 h, then saturated aqueous sodium carbonate solution was added, and the aqueous layer was extracted twice
- 10 with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The residue was purified twice by silica gel chromatography (Gradient: 0% to 4% MeOH in dichloromethane), to afford **C27** as a solid. Yield: 1.12 g, 2.82 mmol, 67%. LCMS  $m/z$  398.3 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  1.36 (d,  $J=6.6$  Hz, 3H),
- 15 1.90 (m, 2H), 2.29 (m, 2H), 3.10 (s, 3H), 3.39 (dd,  $J=8.3, 5.4$  Hz, 1H), 3.44 (dd,  $J=8.4, 5.3$  Hz, 1H), 3.62 (m, 3H), 3.76 (br dd,  $J=7.4, 7.4$  Hz, 1H), 3.84 (br dd,  $J=7.4, 7.4$  Hz, 1H), 4.10 (br d,  $J=11.6$  Hz, 2H), 4.97 (tt,  $J=11.6, 4.2$  Hz, 1H), 5.15 (m, 1H), 8.03 (s, 1H).

- Step 5. Synthesis of title compound **5**. Compound **C27** (50 mg, 0.13 mmol),
- 20 2-fluoro-5-hydroxybenzonitrile (34.5 mg, 0.25 mmol) and potassium carbonate (52.2 mg, 0.38 mmol) were combined in acetonitrile (5 mL), and the mixture was heated at reflux for about 18 h. Removal of solvents *in vacuo* provided a residue which was purified by silica gel chromatography (Gradient: 1% to 3% MeOH in dichloromethane) to provide **5** as a solid. Yield: 19 mg, 0.043
- 25 mmol, 33%. LCMS  $m/z$  439.3 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  1.37 (d,  $J=6.6$  Hz, 3H), 1.89 (m, 2H), 2.29 (dddd,  $J=12, 12, 12, 5$  Hz, 2H), 3.28 (dd,  $J=8.3, 5.4$  Hz, 1H), 3.35 (m, 1H), 3.61 (m, 3H), 3.86 (br dd,  $J=7, 7$  Hz, 1H), 3.92 (br dd,  $J=7, 7$  Hz, 1H), 4.09 (br dd,  $J=11.6, 3.7$  Hz, 2H), 4.90 (m, obscured by water peak, 1H assumed), 4.98 (tt,  $J=11.6, 4.3$  Hz, 1H), 7.19 (m,
- 30 2H), 7.28 (m, 1H), 8.03 (s, 1H).

## Example 6

1-Cyclopentyl-6-[(1*R*)-1-(3-pyrimidin-2-ylazetidin-1-yl)ethyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one



5 Step 1. Preparation of (1*S*)-1-(1-cyclopentyl-4-oxo-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)ethyl methanesulfonate (**C32**).

A. Preparation of 5-amino-1-cyclopentyl-1*H*-pyrazole-4-carbonitrile (**C28**). A solution of cyclopentylhydrazine dihydrochloride (50.9 g, 0.294 mol) in anhydrous EtOH (640 mL) was cooled to 0°C and treated with sodium ethoxide (40.0 g, 0.588 mol) in portions over 2 h. The mixture was stirred at  
10 0°C for 45 mins, then treated drop-wise with a solution of

(ethoxymethylene)malononitrile (35.9 g, 0.294 mol) in EtOH over 1 h. Following the addition, the reaction was stirred at 0°C for 30 mins, then warmed to room temperature over 1 h. The mixture was heated at reflux for 2 h, cooled to room temperature and concentrated *in vacuo*, after which the  
5 residue was mixed with water, and the resulting suspension was filtered. The collected solids were washed three times with water, then three times with a 1:1 mixture of diethyl ether and hexanes, providing **C28** as a beige solid. Yield: 44.0 g, 0.250 mol, 85%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.69 (m, 2H), 1.92 (m, 2H), 2.06 (m, 4H), 4.34 (m, 1H), 7.50 (s, 1H).

10 B. Preparation of 5-amino-1-cyclopentyl-1*H*-pyrazole-4-carboxamide (**C29**). Compound **C28** (44.0 g, 0.250 mol) was added portion-wise to concentrated sulfuric acid (200 mL) at 0°C. After completion of the addition, the reaction mixture was allowed to warm from 0°C to room temperature and stirred for about 18 h. The reaction mixture was poured onto ice, and then  
15 brought to pH 9-10 by addition of concentrated aqueous ammonium hydroxide solution. The resulting solids were collected by filtration, washed three times with water, then washed three times with a 1:1 mixture of diethyl ether and hexanes to provide **C29** as an off-white solid. Yield: 39.8 g, 0.205 mol, 82%. LCMS *m/z* 195.4 (M+1). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.57 (m, 2H), 1.80  
20 (m, 4H), 1.92 (m, 2H), 4.52 (m, 1H), 6.15 (s, 2H), 6.61 (br s, 1H), 7.15 (br s, 1H), 7.62 (s, 1H).

C. Preparation of (1*S*)-2-[(4-carbamoyl-1-cyclopentyl-1*H*-pyrazol-5-yl)amino]-1-methyl-2-oxoethyl acetate (**C30**). (1*S*)-2-Chloro-1-methyl-2-oxoethyl acetate (12 mL, 95 mmol) was slowly added drop-wise to an ice-cooled suspension of **C29** (16.4 g, 84.4 mmol) in anhydrous 1,4-dioxane (200 mL). After being stirred at 0°C for 40 mins, the reaction mixture was heated at reflux for 2 h. It was then cooled to room temperature and concentrated *in vacuo*, to afford **C30**, which was used directly in the next step.  
25

D. Preparation of 1-cyclopentyl-6-[(1*S*)-1-hydroxyethyl]-1,5-dihydro-  
30 4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (**C31**). Compound **C30** from the previous step (assumed 84.4 mmol) was dissolved in a mixture of water (200 mL) and

THF (20 mL). To this solution was added potassium carbonate (60 g, 0.43 mol), and the resulting mixture was heated at 50°C for 2 days. The reaction mixture was cooled to room temp and extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and concentrated *in vacuo* to provide **C31** as a tan solid. Yield: 17.5 g, 70.5 mmol, 84% over 2 steps. LCMS *m/z* 249.4 (M+1). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.41 (d, *J*=6.6 Hz, 3H), 1.67 (m, 2H), 1.90 (m, 4H), 2.06 (m, 2H), 4.61 (q, *J*=6.6 Hz, 1H), 5.13 (m, 1H), 8.02 (s, 1H).

E. Preparation of **C32**. A solution of **C31** (93% purity by weight, 87.74 g, 328.6 mmol) in 2-methyltetrahydrofuran (408 mL) was treated with 4-methylmorpholine (54.4 mL, 495 mmol), followed, after 5 mins, by methanesulfonyl chloride (26.7 mL, 345 mmol). The temperature of the reaction was maintained between 25 and 40°C for 3 h. After cooling to room temp, the reaction mixture was filtered through Celite to remove morpholine salts, and the filter cake was washed with 5-10 volumes of 2-methyltetrahydrofuran. The filtrate was concentrated *in vacuo*, then purified by silica gel chromatography (Eluant: 9:1 EtOAc: hexanes). Pure fractions were combined and concentrated to afford **C32** as a slightly yellow solid. Yield: 48.6 g, 149 mmol, 45%. Mixed fractions were combined and concentrated to provide 40 grams of a residue which was purified by trituration with methyl *tert*-butyl ether (100 mL) to provide additional **C32** as a white solid. Combined yield: 79.5 g, 244 mmol, 74%. LCMS *m/z* 325.1 (M-1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.75 (m, 2H), 1.86 (d, *J*=6.8 Hz, 3H), 1.99 (m, 2H), 2.13 (m, 4H), 3.23 (s, 3H), 5.18 (m, 1H), 5.70 (q, *J*=6.7 Hz, 1H), 8.07 (s, 1H), 11.04 (br s, 1H).

Step 2. Preparation of 2-azetidin-3-ylpyrimidine dimethanesulfonate (**C34**).

A. Preparation of *tert*-butyl 3-pyrimidin-2-ylazetidine-1-carboxylate (**C33**). Zinc powder (150.1 g, 2.30 mol) and molecular sieves (50 g) were combined in a reaction flask and flame-dried under vacuum for 10 mins. Once the flask had returned to room temperature, it was charged with THF (4

L), and 1,2-dibromoethane (24.4 mL, 0.28 mol) was added. The reaction mixture was heated to 50°C for 10 mins, then allowed to come to ambient temperature, at which time trimethylsilyl chloride (33.5 mL, 0.264 mol) was added {*Caution: slightly exothermic*}. The mixture was allowed to stir at room temperature for about 18 h. Slow addition of **C7** (500 g, 1.77 mol) over 1.5 h was followed by stirring for an additional 18 h. In a separate flask, 2-bromopyrimidine (253 g, 1.59 mol) was combined with molecular sieves (85 g) in THF (1.3 L), and the mixture was degassed. This mixture was treated with tetrakis(triphenylphosphine)palladium(0) (32.7 g, 0.0283 mol), then added to the flask containing the reaction mixture from **C7**. The reaction was stirred for 25 h, and then filtered through Celite. The filtrate was concentrated under reduced pressure, then partitioned between saturated aqueous sodium carbonate solution (2 L) and EtOAc (2 L). The aqueous layer was extracted with EtOAc (2 x 2 L), and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The resulting yellow liquid residue was triturated with methyl *tert*-butyl ether (500 mL), and the precipitate was removed by filtration. Partial concentration of the filtrate resulted in precipitation of a solid; the mixture at this point was cooled in an ice-water bath. Filtration then provided a solid, which was washed with a minimum quantity of cold methyl *tert*-butyl ether to afford **C33** as a white solid, which was taken directly into the next step. Yield: 131 g, 0.557 mol, 31%. GCMS *m/z* 180 ([M - *tert*-butyl]+1); 136 ([M - BOC]+1). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.45 (s, 9H), 4.0 (m, 1H), 4.3 (m, 4H), 7.2 (t, 1H), 8.75 (d, 2H).

B. Preparation of compound **C34**. Methanesulfonic acid (108.3 mL, 1.67 mol) was added to an ice-cold solution of **C33** (131 g, 0.557 mol, from previous step) in dichloromethane:dioxane (9:1 ratio, 1 L). The mixture was allowed to warm to room temperature over about 18 h, with stirring. The precipitate was filtered and washed with methyl *tert*-butyl ether to provide **C34** as a white solid. Yield: 180 g, 0.550 mol, 99%. LCMS *m/z* 136.2 (M+1). <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O) δ 2.55 (s, 6H), 4.33 (m, 5H), 7.64 (t, *J*=5.3 Hz, 1H),

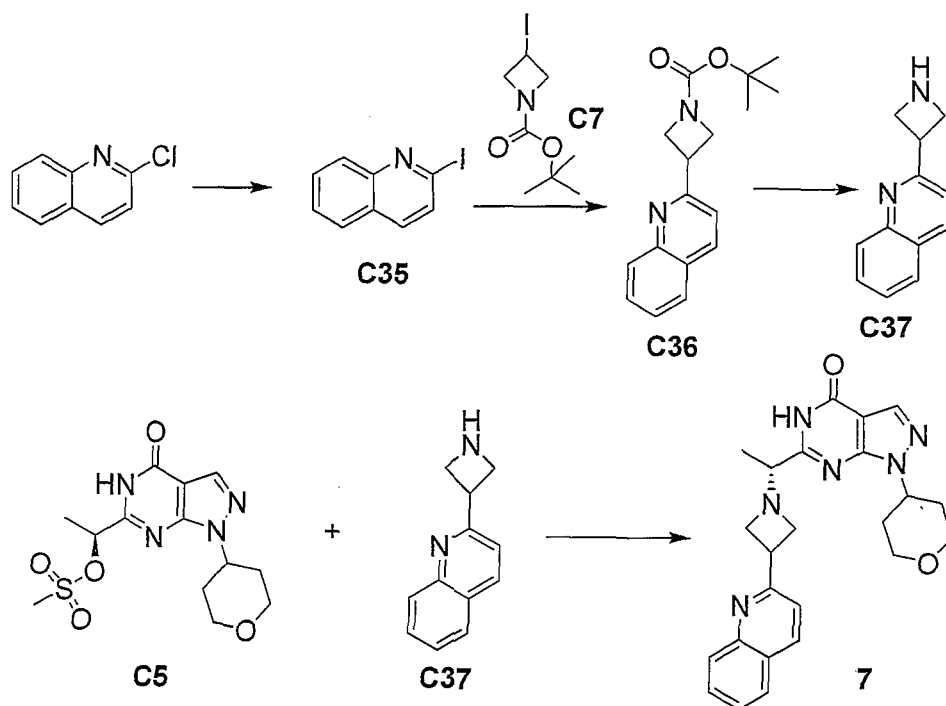


8.90 (d,  $J=5.2$  Hz, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{D}_2\text{O}$ )  $\delta$  36.47, 38.53, 49.98, 121.63, 158.08, 164.37.

Step 3. Synthesis of title compound **6**. Compounds **C32** (35 g, 107 mmol) and **C34** (38.62 g, 118 mmol) were mixed with acetonitrile (700 mL), and the  
5 heterogeneous reaction mixture was treated with triethylamine (134 mL, 961 mmol) and heated to 80°C for 3.5 h. The reaction became homogeneous and light yellow. The product was concentrated by distillation at a pot temperature of 80-90°C, until 350-500 mL of acetonitrile remained. It was then allowed to crystallize as it cooled to room temperature. The mixture was stirred for about  
10 18 h and then filtered to obtain **6** as a solid. Yield: 21 g, 57.5 mmol, 54%. For samples of **6** prepared under similar conditions, but chromatographed rather than crystallized, the minor enantiomer of the product was removed by chiral chromatography using a Chiralpak AD-H column (5  $\mu\text{m}$ ; 2.1 x 25 cm; mobile phase: 70:30 carbon dioxide: MeOH; flow rate 65 g/min). Compound  
15 **6** was the second-eluting enantiomer, retention time approximately 3.35 min. LCMS  $m/z$  366.2 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.33 (d,  $J=6.6$  Hz, 3H), 1.72 (m, 2H), 1.97 (m, 2H), 2.11 (m, 4H), 3.58 (m, 2H), 3.71 (dd,  $J=7.1$ , 7.1 Hz, 1H), 3.79 (m, 2H), 4.00 (m, 1H), 5.16 (m, 1H), 7.19 (t,  $J=4.9$  Hz, 1H), 8.05 (s, 1H), 8.72 (d,  $J=5.0$  Hz, 2H), 9.86 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$   
20 18.07, 24.73, 32.38, 32.45, 37.61, 56.69, 57.69, 57.78, 65.09, 105.09, 119.00, 134.54, 157.11, 157.93, 160.39, 169.82 (one aromatic signal not observed).

Example 7

6-[(1*R*)-1-(3-Quinolin-2-ylazetidin-1-yl)ethyl]-1-(tetrahydro-2*H*-pyran-4-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one



5 Step 1. Preparation of 2-azetidin-3-ylquinoline (C37).

A. Preparation of 2-iodoquinoline (C35). 2-Chloroquinoline (8.18 g, 50.0 mmol), trimethylsilyl chloride (98%, 6.48 mL, 50.0 mmol) and sodium iodide (98%, 15.3 g, 100 mmol) were mixed with propionitrile (50 mL) and heated at reflux for about 18 h. The reaction was then cooled to room temperature and quenched with aqueous sodium hydroxide solution (1N, 25 mL). After extraction with EtOAc, the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification via silica gel chromatography (Gradient: 0-100% ethyl acetate in heptane) afforded C35. Yield: 5.33 g, 20.9 mmol, 42%. LCMS *m/z* 255.9 (M+1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.57 (ddd, *J*=8.1, 6.9, 1.2 Hz, 1H), 7.75 (m, 4H), 8.05 (br d, *J*=8.5 Hz, 1H).

B. Preparation of *tert*-butyl 3-quinolin-2-ylazetidine-1-carboxylate (C36). Compound C36 was prepared according to the general procedure for the synthesis of C8 in Example 1, except that C35 was used in place of 2-

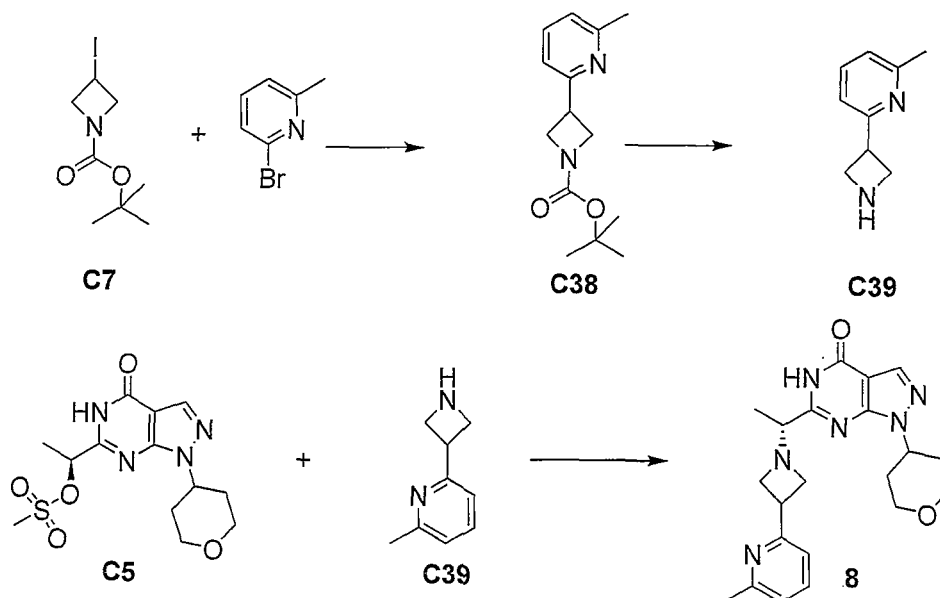
bromo-4-methylpyridine, and the reaction was stirred at 50°C for 18 h after addition of the palladium catalyst and **C35**. Purification was carried out via silica gel chromatography (Gradient 0-100% EtOAc in heptane) to provide **C36**. Yield: 1.05 g, 3.69 mmol, 47%. LCMS  $m/z$  285.1 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.48 (s, 9H), 4.07 (m, 1H), 4.30 (dd,  $J=8.6, 5.9$  Hz, 2H), 4.41 (dd,  $J=8.7, 8.7$  Hz, 2H), 7.43 (d,  $J=8.5$  Hz, 1H), 7.53 (ddd,  $J=8.1, 6.9, 1.1$  Hz, 1H), 7.72 (ddd,  $J=8.4, 6.9, 1.4$  Hz, 1H), 7.81 (br d,  $J=8.1$  Hz, 1H), 8.07 (br d,  $J=8.5$  Hz, 1H), 8.16 (d,  $J=8.5$  Hz, 1H).

C. Preparation of **C37**. A solution of **C36** (1.0 g, 3.5 mmol) in methanolic hydrochloric acid (1.25M, 50 mL, 62 mmol) was stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo*, and extracted with dichloromethane after conversion of product to the free base with 6N aqueous sodium hydroxide solution. Removal of solvent *in vacuo* provided **C37**. Yield: 310 mg, 1.68 mmol, 48%. LCMS  $m/z$  185.2 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  3.80 (dd,  $J=8.0, 8.0$  Hz, 2H), 3.91 (dd,  $J=7.4, 7.4$  Hz, 2H), 4.16 (m, 1H), 7.54 (d,  $J=8.3$  Hz, 1H), 7.56 (ddd,  $J=8.1, 6.9, 1.1$  Hz, 1H), 7.74 (ddd,  $J=8.4, 6.9, 1.6$  Hz, 1H), 7.96 (m, 2H), 8.32 (d,  $J=8.5$  Hz, 1H).

Step 2. Synthesis of title compound **7**. Compound **7** was prepared according to the general procedure for the synthesis of **1** in Example 1, except that **C37** was used in place of **C9**, and the chromatography was carried out with a gradient of 0-10% EtOAc in EtOH, to afford **7** as a glass. Yield: 480 mg, 1.11 mmol, 79%. LCMS  $m/z$  431.1 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.38 (d,  $J=6.6$  Hz, 3H), 1.93 (br d,  $J=12.6$  Hz, 2H), 2.39 (m, 2H), 3.63 (m, 4H), 3.79 (m, 1H), 3.87 (m, 2H), 4.06 (m, 1H), 4.15 (m, 2H), 4.86 (tt,  $J=11.7, 4$  Hz, 1H), 7.40 (d,  $J=8.3$  Hz, 1H), 7.54 (ddd,  $J=8.1, 6.9, 1.2$  Hz, 1H), 7.73 (ddd,  $J=8.4, 6.9, 1.4$  Hz, 1H), 7.82 (dd,  $J=8.2, 1.1$  Hz, 1H), 8.08 (s, 1H), 8.09 (d,  $J=8.3$  Hz, 1H), 8.15 (d,  $J=8.5$  Hz, 1H).

Example 8

6-[(1*R*)-1-[3-(6-Methylpyridin-2-yl)azetidin-1-yl]ethyl]-1-(tetrahydro-2*H*-pyran-4-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one



5 Step 1. Preparation of 2-azetidin-3-yl-6-methylpyridine (**C39**).

A. Preparation of *tert*-butyl 3-(6-methylpyridin-2-yl)azetidine-1-carboxylate (**C38**). Compound **C38** was prepared according to the general procedure for the synthesis of **C8** in Example 1, except that 2-bromo-6-methylpyridine was used in place of 2-bromo-4-methyl pyridine. Yield: 397  
 10 mg, 1.60 mmol, 45%. LCMS *m/z* 249.2 (*M*+1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.46 (s, 9H), 2.54 (s, 3H), 3.85 (tt, *J*=8.8, 6.1 Hz, 1H), 4.13 (dd, *J*=8.6, 6.1 Hz, 2H), 4.30 (dd, *J*=8.8, 8.8 Hz, 2H), 7.02 (d, *J*=7.7 Hz, 1H), 7.08 (d, *J*=7.9 Hz, 1H), 7.55 (dd, *J*=7.7, 7.7 Hz, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 24.72, 28.65, 35.42, 55.2 (v broad), 79.61, 118.32, 121.61, 137.05, 156.75, 158.39, 160.60.

15 B. Preparation of compound **C39**. Compound **C39** was prepared according to the general procedure for the synthesis of **C9** in Example 1, except that **C38** was used instead of **C8**. Yield: 74.1 mg, 0.50 mmol, 100%. LCMS *m/z* 149.1 (*M*+1).

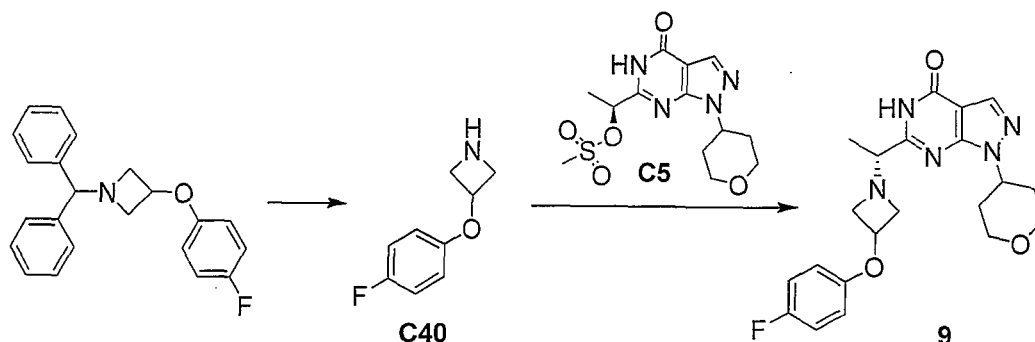
20 Step 2. Synthesis of compound **8**. Compound **8** was prepared according to the general procedure for the synthesis of **1** in Example 1, except that **C39** was used instead of **C9**. Compound **8** was isolated as an off-white solid.

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Yield: 41 mg, 0.104 mmol, 31%. LCMS  $m/z$  395.1 (M+1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.33 (d,  $J=6.6$  Hz, 3H), 1.91 (br d,  $J=12.6$  Hz, 2H), 2.38 (m, 2H), 2.54 (s, 3H), 3.45 (dd,  $J=6.5$ , 6.5 Hz, 1H), 3.55-3.65 (m, 4H), 3.72-3.85 (m, 3H), 4.14 (dd,  $J=11.4$ , 3.9 Hz, 2H), 4.84 (tt,  $J=11.6$ , 4.2 Hz, 1H), 7.02 (d,  $J=7.7$  Hz, 1H), 7.05 (d,  $J=7.7$  Hz, 1H), 7.53 (dd,  $J=7.7$ , 7.7 Hz, 1H). 8.06 (s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  18.19, 24.54, 32.17, 36.64, 53.69, 57.53, 58.65, 65.16, 67.01, 105.31, 118.39, 121.25, 134.72, 136.64, 151.89, 157.86, 158.08, 159.73, 160.80.

### Example 9

10 6-((1R)-1-[3-(4-Fluorophenoxy)azetidin-1-yl]ethyl)-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Step 1. Preparation of 3-(4-fluorophenoxy)azetidine (**C40**). Palladium hydroxide (500 mg) and 1-(diphenylmethyl)-3-(4-fluorophenoxy)azetidine (500 mg, 1.50 mmol) were combined in ethanol (50 mL) and hydrogenated at 50 psi for 18 h. The reaction mixture was then filtered through Celite and concentrated *in vacuo*. The residue was purified via silica gel chromatography (Eluant: 00:5:2 chloroform: MeOH: concentrated aqueous ammonium hydroxide) to provide **C40**. Yield: 188 mg, 1.12 mmol, 75%.  
 15 LCMS  $m/z$  168.1 (M+1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.44 (br s, 1H), 3.76 (m, 2H), 3.89 (m, 2H), 4.91 (m, 1H), 6.66 (m, 2H), 6.93 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  54.55, 70.81, 115.43, 115.51, 115.76, 115.99, 152.96, 156.15, 158.53.

Step 2. Synthesis of title compound **9**. Compound **9** was prepared according to the general procedure for the synthesis of **1** in Example 1, except that **C40**  
 25

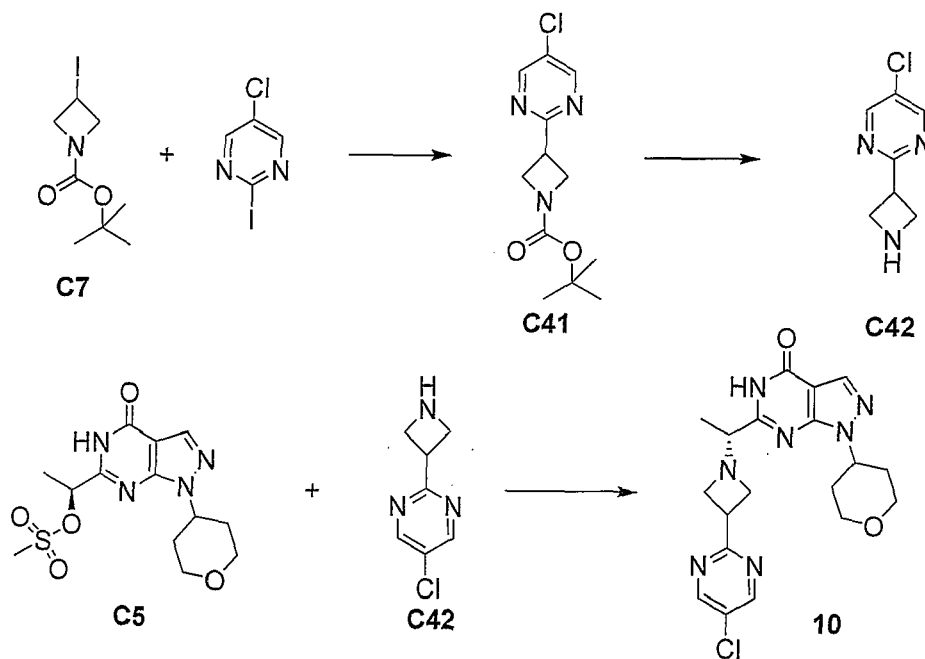
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was used in place of **C9**. Yield: 258 mg, 0.624 mmol, 85%. LCMS  $m/z$  414.4 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.36 (d,  $J=6.6$  Hz, 3H), 1.91 (br d,  $J=12.6$  Hz, 2H), 2.37 (m, 2H), 3.23 (br s, 1H), 3.40 (m, 1H), 3.61 (m, 3H), 3.88 (br s, 2H), 4.14 (dd,  $J=11.5, 4.0$  Hz, 2H), 4.75-4.88 (m, 2H), 6.71 (m, 2H), 6.97 (m, 2H), 8.06 (s, 1H). This material (80% ee) was subjected to chromatography using a Chiralpak AS-H column (Eluant: 85:15 carbon dioxide: MeOH), followed by silica gel chromatographic purification (Eluant: 100:1 chloroform: MeOH) to provide the pure enantiomer **9**. Yield: 102 mg. Enantiomeric excess: 100%; LCMS and  $^1\text{H}$  NMR essentially unchanged.

10

Example 10

6-[(1*R*)-1-[3-(5-Chloropyrimidin-2-yl)azetidin-1-yl]ethyl]-1-(tetrahydro-2*H*-pyran-4-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one



Step 1. Preparation of 2-azetidin-3-yl-5-chloropyrimidine (**C42**).

15

A. Preparation of *tert*-butyl 3-(5-chloropyrimidin-2-yl)azetidine-1-carboxylate (**C41**). Compound **C41** was prepared according to the general procedure for the synthesis of **C8** in Example 1, except that 5-chloro-2-iodopyrimidine was used in place of 2-bromo-4-methyl pyridine, the reaction was carried out at room temperature, and the chromatographic purification was carried out using 1:4 EtOAc: heptane. Yield: 1.13 g, 4.19 mmol, 42%.

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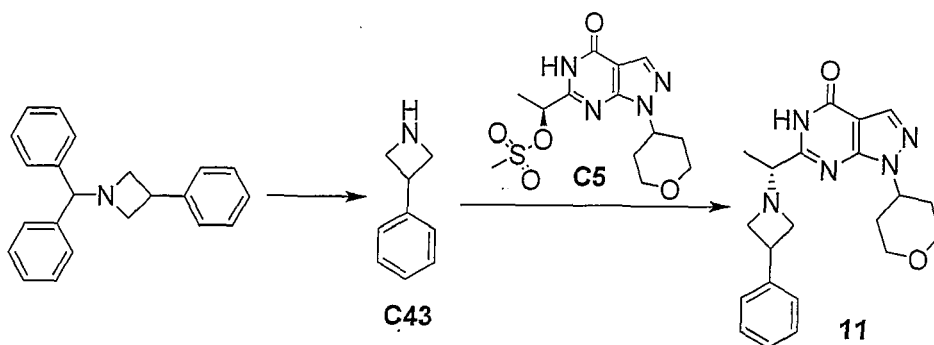
LCMS  $m/z$  270.1 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.44 (s, 9H), 4.00 (tt,  $J=8.8, 6.0$  Hz, 1H), 4.21 (dd,  $J=8.5, 6.0$  Hz, 2H), 4.31 (dd,  $J=8.7, 8.7$  Hz, 2H), 8.66 (s, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  28.32, 35.59, 54.0 (br), 79.48, 129.47, 155.69, 156.32, 168.01.

- 5           B. Synthesis of compound **C42**. Compound **C42** was prepared according to the general procedure for the synthesis of **C9** in Example 1, except that **C41** was used instead of **C8**. Yield: 170 mg, 1.00 mmol, 100%. LCMS  $m/z$  170.1 ( $M+1$ ).

- Step 2. Synthesis of title compound **10**. Compound **10** was prepared according to the general procedure for the synthesis of **1** in Example 1, except that **C42** was used in place of **C9**. Yield: 240 mg, 0.577 mmol, 86%. LCMS  $m/z$  416.0 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.33 (d,  $J=6.8$  Hz, 3H), 1.91 (br d,  $J=12.6$  Hz, 2H), 2.38 (m, 2H), 3.52-3.64 (m, 4H), 3.68 (dd,  $J=7.3, 7.3$  Hz, 1H), 3.78 (dd,  $J=7.7, 7.7$  Hz, 2H), 3.99 (m, 1H), 4.14 (dd,  $J=11.3, 4.0$  Hz, 2H), 4.83 (tt,  $J=11.6, 4.2$  Hz, 1H), 8.06 (s, 1H), 8.67 (s, 2H), 9.9 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  18.02, 32.18, 37.06, 53.76, 56.80, 57.83, 65.02, 67.03, 105.32, 129.44, 134.74, 151.88, 155.60, 157.81, 160.52, 167.62.

### Example 11

- 20           6-[1(1*R*)-1-(3-Phenylazetidin-1-yl)ethyl]-1-(tetrahydro-2*H*-pyran-4-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one

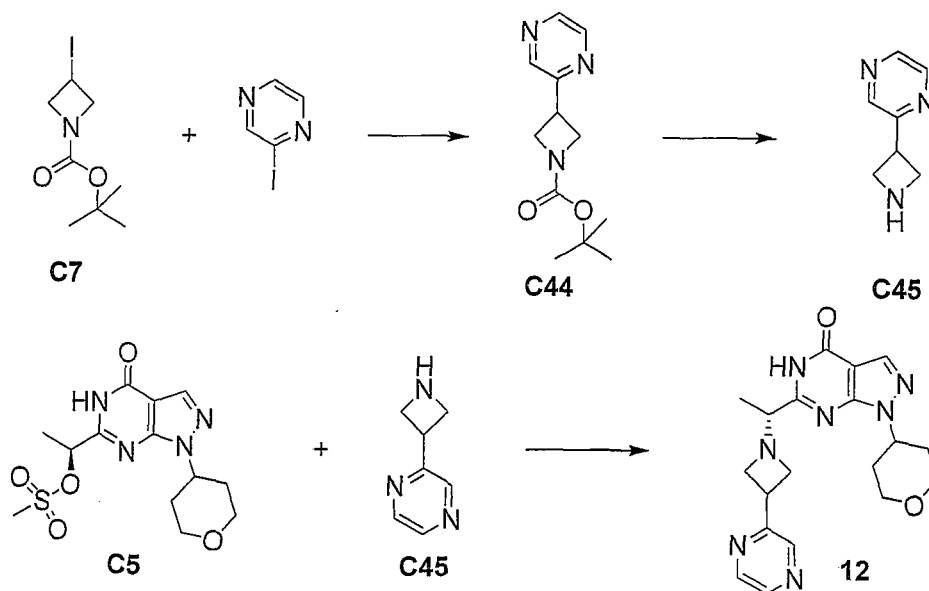


- Step 1. Preparation of 3-phenylazetidine (**C43**). Compound **C43** was prepared according to the general procedure for the synthesis of **C40** in Example 9, except that 1-(diphenylmethyl)-3-phenylazetidine (See M.C. Hillier & C-y. Chen, *J. Organic Chem.* 2006, 71, 7885-7887) was used instead of 1-(diphenylmethyl)-3-(4-fluorophenoxy)azetidine, and the silica gel

chromatography was carried out with 100:5:1 chloroform: MeOH: concentrated aqueous ammonium hydroxide as eluant. Yield: 427 mg (contains some impurities), <3.21 mmol, <19%. LCMS  $m/z$  134.0 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ), product peaks only:  $\delta$  4.02 (m, 2H), 4.11 (m, 3H),  
5 7.29 (m, 5H).

Step 2. Synthesis of title compound **11**. Compound **11** was prepared according to the general procedure for the synthesis of **1** in Example 1, except that **C43** was used in place of **C9**, and the chromatographic purification was carried out with 200:1 chloroform: MeOH as eluant. Yield: 485 mg, 1.28  
10 mmol, 67%. Enantiomeric excess: 89.5%. LCMS  $m/z$  380.2 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.34 (d,  $J=6.6$  Hz, 3H), 1.92 (br d,  $J=12.6$  Hz, 2H), 2.39 (m, 2H), 3.25 (dd,  $J=5.6, 5.6$  Hz, 1H), 3.38 (dd,  $J=5.8, 5.8$  Hz, 1H), 3.51 (q,  $J=6.7$  Hz, 1H), 3.62 (m, 2H), 3.79 (m, 3H), 4.15 (br dd,  $J=11.5, 3.4$  Hz, 2H), 4.84 (tt,  $J=11.6, 4.2$  Hz, 1H), 7.23-7.37 (m, 5H), 8.07 (s, 1H), 9.87 (br s, 1H).  
15  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  18.23, 32.17, 34.96, 53.72, 59.03, 60.24, 65.43, 67.01, 105.31, 126.80, 128.56, 134.74, 141.41, 151.83, 157.78, 160.56 (one aromatic signal not observed). This material was subjected to chiral chromatography (column: Chiralpak AD-H, 2.1 x 25 cm; Mobile phase: 85:15 carbon dioxide: MeOH; flow rate 65 g/min) to provide the pure enantiomer **11**.  
20 Yield: 333 mg. Enantiomeric excess: 100%; LCMS and  $^1\text{H}$  NMR essentially unchanged.



Example 126-[(1*R*)-1-(3-Pyrazin-2-ylazetidin-1-yl)ethyl]-1-(tetrahydro-2*H*-pyran-4-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one5 Step 1. Preparation of 2-azetidin-3-ylpyrazine (**C45**).

A. Preparation of *tert*-butyl 3-pyrazin-2-ylazetidine-1-carboxylate (**C44**). Compound **C44** was prepared according to the general procedure for the synthesis of **C8** in Example 1, except that 2-iodopyrazine was used in place of 2-bromo-4-methylpyridine. Yield: 360 mg, 1.53 mmol, 43%. LCMS *m/z* 236.2 (*M*+1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.46 (s, 9H), 3.91 (tt, *J*=8.7, 5.9 Hz, 1H), 4.18 (dd, *J*=8.5, 6.0 Hz, 2H), 4.32 (dd, *J*=8.7, 8.7 Hz, 2H), 8.47 (d, *J*=2.5 Hz, 1H), 8.50 (d, *J*=1.7 Hz, 1H), 8.60 (dd, *J*=2.5, 1.5 Hz, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 28.35, 32.59, 54.55 (br), 79.63, 143.17, 143.70, 144.52, 156.30 (one downfield signal not observed).

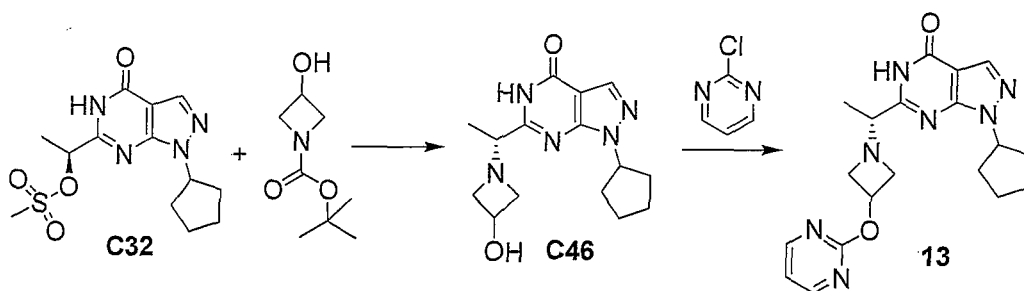
15 B. Preparation of **C45**. Compound **C45** was prepared according to the general procedure for the synthesis of **C9** in Example 1, except that **C44** was used instead of **C8**. Yield: 67.6 mg, 0.500 mmol, 100%. LCMS *m/z* 136.1 (*M*+1).

20 Step 2. Synthesis of title compound **12**. Compound **12** was prepared according to the general procedure for the synthesis of **1** in Example 1, except that **C45** was used in place of **C9**, and the chromatographic purification was

carried out with 200:1, then 100:1 chloroform: MeOH as eluant. MS (APCI)  $m/z$  382.2 (M+1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.35 (d,  $J=6.6$  Hz, 3H), 1.90 (br d,  $J=12.5$  Hz, 2H), 2.36 (m, 2H), 3.50 (dd,  $J=7.0$ , 7.0 Hz, 1H), 3.56-3.67 (m, 4H), 3.81 (m, 2H), 3.93 (m, 1H), 4.13 (br dd,  $J=11.5$ , 3.6 Hz, 2H), 4.84 (tt,  $J=11.7$ , 4.2 Hz, 1H), 8.05 (s, 1H), 8.46 (d,  $J=2.5$  Hz, 1H), 8.51 (d,  $J=1.7$  Hz, 1H), 8.57 (dd,  $J=2.5$ , 1.7 Hz, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  17.92, 32.15, 34.10, 53.73, 56.95, 58.35, 64.93, 66.98, 105.25, 134.69, 143.10, 143.93, 144.23, 151.79, 155.54, 157.98, 160.19.

### Example 13

#### 10 1-Cyclopentyl-6-[(1*R*)-1-[3-(pyrimidin-2-yloxy)azetidin-1-yl]ethyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one



Step 1. Preparation of 1-cyclopentyl-6-[(1*R*)-1-(3-hydroxyazetidin-1-yl)ethyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (**C46**). Compound **C46** was prepared according to the general procedure for the synthesis of **C19** in Example 3, except that **C32** was used in place of **C18**. Yield: 2.0 g, 6.6 mmol, 69%. MS (APCI)  $m/z$  302.0 (M-1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.33 (d,  $J=6.6$  Hz, 3H), 1.71 (m, 2H), 1.97 (m, 2H), 2.10 (m, 4H), 3.18 (m, 1H), 3.28 (m, 1H), 3.51-3.65 (m, 3H), 4.44 (m, 1H), 5.17 (m, 1H), 8.09 (s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  18.25, 24.69, 32.41, 57.75, 61.87, 62.15, 62.57, 64.63, 104.92, 134.62, 152.11, 159.04, 160.41.

Step 2. Synthesis of title compound **13**. Compound **13** was prepared according to the general procedure for the synthesis of **3** in Example 3, except that **C46** was used instead of **C19**. Yield: 130 mg, 0.34 mmol, 21%. LCMS  $m/z$  382.3 (M+1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.34 (d,  $J=6.6$  Hz, 3H), 1.70 (m, 2H), 1.94 (m, 2H), 2.08 (m, 4H), 3.25 (br s, 1H), 3.42 (br s, 1H), 3.56 (br s,

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1H), 3.92 (br s, 2H), 5.15 (m, 1H), 5.27 (m, 1H), 6.96 (t,  $J=4.8$  Hz, 1H), 8.03 (s, 1H), 8.49 (d,  $J=4.8$  Hz, 2H), 9.89 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  18.02, 24.68, 32.36, 57.71, 58.44, 60.22, 65.14 (br), 65.31, 105.02, 115.58, 134.51, 151.93, 157.89, 159.38, 163.99 (one aromatic signal not observed).

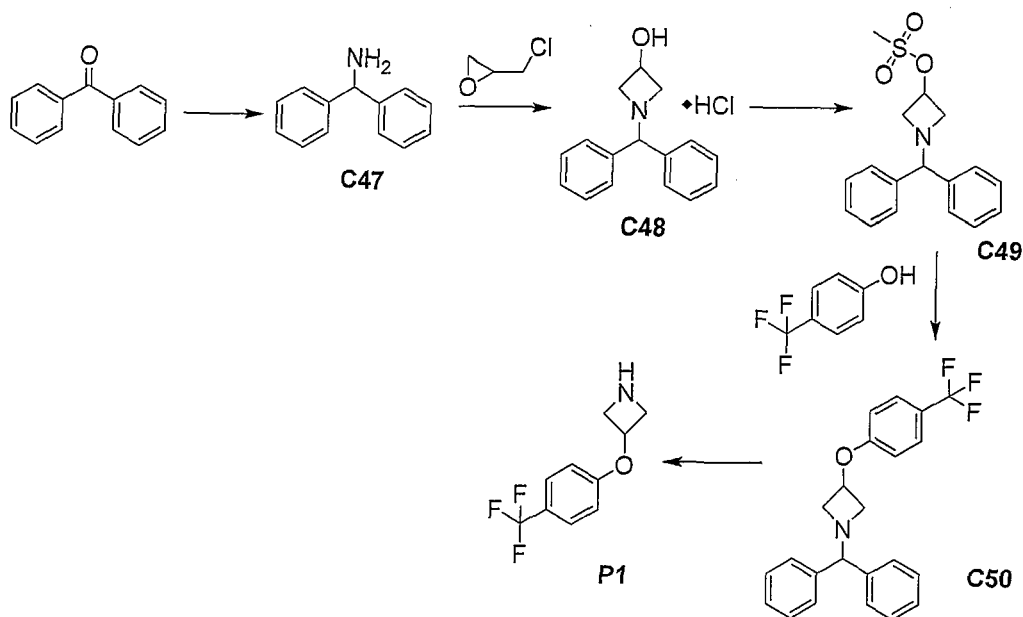
- 5 This material (85% ee) was subjected to chromatography using a Chiralpak AS-H column (Eluant: 90:10 carbon dioxide: MeOH), followed by silica gel chromatographic purification (Eluant: 100:1 chloroform: MeOH) to provide the pure enantiomer **13**. Yield: 68 mg. LCMS  $m/z$  382.3 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.37 (br s, 3H), 1.72 (m, 2H), 1.96 (m, 2H), 2.10 (m, 4H), 3.30 (br s, 1H), 3.47 (br s, 1H), 3.60 (br s, 1H), 3.96 (br s, 2H), 5.16 (m, 1H), 5.29 (m, 1H), 6.98 (t,  $J=4.8$  Hz, 1H), 8.05 (s, 1H), 8.50 (d,  $J=4.8$  Hz, 2H), 9.87 (br s, 1H).
- 10

#### Additional Examples

- Side chains used in the synthesis of the compounds of Examples 14-15 87 (as shown in Table 2 below) that were not commercially available were prepared according to the following methods:

#### Preparation 1

##### Preparation of 3-(4-trifluoromethylphenoxy)azetidine



A. Preparation of 1,1-diphenylmethanamine (**C47**). A mixture of benzophenone (250 g, 1.37 mol), formamide (250 mL) and 85% formic acid (31.5 mL) was heated to 190°C for 3 h. The reaction mixture was cooled to 140°C and poured into cold water (1.2 L). The resulting precipitate was  
5 collected by filtration, to which was added concentrated aqueous hydrochloric acid (600 mL), and the reaction mixture was heated at reflux under vigorous stirring. The hydrochloride salt was collected by filtration and washed with water, then with diethyl ether. The white crystals were treated with a 2.5N aqueous solution of sodium hydroxide and extracted with diethyl ether. The  
10 combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was distilled under reduced pressure to afford **C47** as a colorless oil. Yield: 227.5 g, 1.24 mol, 90%.

B. Preparation of 1-(diphenylmethyl)azetidin-3-ol hydrochloride (**C48**). A solution of 2-(chloromethyl)oxirane (260 g, 2.81 mol) and **C47** (500 g, 2.73  
15 mol) in MeOH (1 L) was heated at reflux for 4 days. Solvent was removed under reduced pressure to provide a white precipitate, which was collected by filtration. The solid was washed with acetone and dried to provide **C48**, which was used in the next step without further purification.

C. Preparation of 1-(diphenylmethyl)azetidin-3-yl methanesulfonate  
20 (**C49**). Methanesulfonyl chloride (180 g, 1.57 mol) was added to a solution of **C48** (360 g, 1.31 mol) and triethylamine (330 g, 3.26 mol) in dichloromethane (3 L) at 0°C. The reaction mixture was stirred at room temperature for 3 h, quenched with saturated aqueous sodium bicarbonate solution, then extracted with dichloromethane. The combined organic layers were dried over  
25 anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford **C49**. Yield: 360 g, 1.14 mol, 87%.

D. Preparation of 1-(diphenylmethyl)-3-[4-(trifluoromethyl)phenoxy]azetidine (**C50**). To a solution of **C49** (317 g, 1.0 mol)  
30 in acetonitrile (1.5 L) were added 4-(trifluoromethyl)phenol (194.4 g, 1.2 mol) and potassium carbonate (165.6 g, 1.2 mol). The reaction mixture was heated at reflux for about 20 h, then the mixture was filtered and concentrated *in*

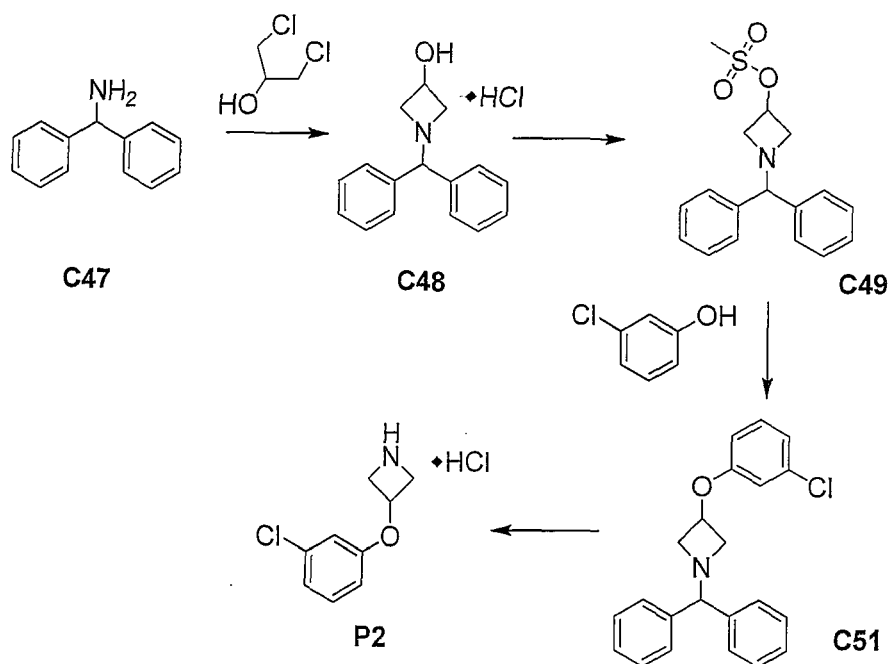
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*vacuo*. Dichloromethane (800 mL) was added, the organic phase was washed with water, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Eluent: 5:1 hexane: diethyl ether) to provide **C50**. Yield: 373 g, 0.97 mol, 97%.

- 5 E. Preparation of compound **P1**. To a solution of **C50** (191 g, 0.50 mol) in MeOH (2 L) was added 10% palladium hydroxide on carbon (9.6 g), and the suspension was hydrogenated at 45 psi at 60°C for about 18 h. The reaction mixture was filtered and the filtrate was concentrated to afford **P1**, which was used in the next step without further purification. Yield: 86.6 g, 0.40
- 10 mol, 80%. LCMS  $m/z$  218.1 (M+1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.85 (m, 2H), 3.96 (m, 2H), 4.99 (m, 1H), 6.77 (d, 2H), 7.50 (m, 2H).

### Preparation 2

#### Preparation of 3-(3-chlorophenoxy)azetidine



- 15 A. Preparation of 1-(diphenylmethyl)azetidin-3-ol hydrochloride (**C48**). Compound **C48** was prepared according to the procedure described in Preparation 1, except that 1,3-dichloropropan-2-ol was used in place of 2-(chloromethyl)oxirane. Yield: 4321 g, 15.7 mol, 48%.

- B. Preparation of 1-(diphenylmethyl)azetidin-3-yl methanesulfonate (**C49**). Compound **C49** was prepared according to the procedure described in
- 20

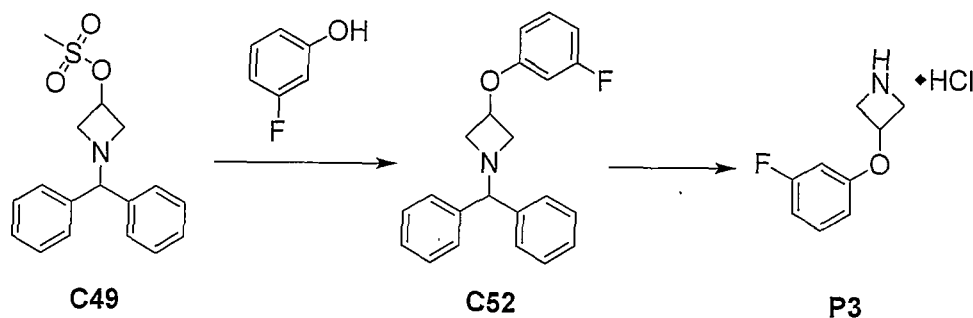
Preparation 1 to afford **C49** as a yellow solid. Yield: 303 g, 0.96 mol, 91%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.91 (s, 3H), 3.13 (m, 2H), 3.55 (m, 2H), 4.31 (s, 1H), 4.02 (m, 1H), 7.14 (m, 2H), 7.20 (m, 4H), 7.31 (m, 4H).

- C. Preparation of 3-(3-chlorophenoxy)-1-(diphenylmethyl)azetidine (**C51**). To a stirred suspension of sodium hydride (60%, dispersed in oil, 25.2 g, 0.63 mol) in DMF (1.5 L) was added 3-chlorophenol (70.88 g, 0.63 mol) at 0°C. After completion of the addition, the reaction mixture was stirred for 1 h, then **C49** (200 g, 0.63 mol) was added in one portion. The reaction was heated at reflux for 3 h, diluted with water and extracted with EtOAc (3 x 1 L).  
The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Eluant: petroleum ether) to afford **C51** as a light yellow solid. Yield: 123 g, 0.35 mol, 51%.

- D. Preparation of compound **P2**. To a solution of **C51** (200 g, 0.569 mol) in dichloromethane (2 L) was added drop-wise 2-chloroethyl chloroformate (75 mL, 0.726 mol) at room temperature. After completion of the addition, the reaction mixture was stirred for 4 h, and concentrated to dryness. The residue was dissolved in MeOH (2 L) and the reaction mixture was heated at reflux for 3 h. The mixture was concentrated *in vacuo* and diethyl ether (500 mL) was added; the resulting precipitate was filtered to give **P2** as a white solid. Yield: 60 g, 0.27 mol, 44.5%. LCMS *m/z* 184.4 (M+1). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.95 (m, 2H), 4.43 (m, 2H), 5.15 (m, 1H), 6.85 (m, 1H), 6.97 (s, 1H), 7.08 (m, 1H), 7.32 (m, 1H), 9.58 (br s, 2H).

### Preparation 3

#### Preparation of 3-(3-fluorophenoxy)azetidine



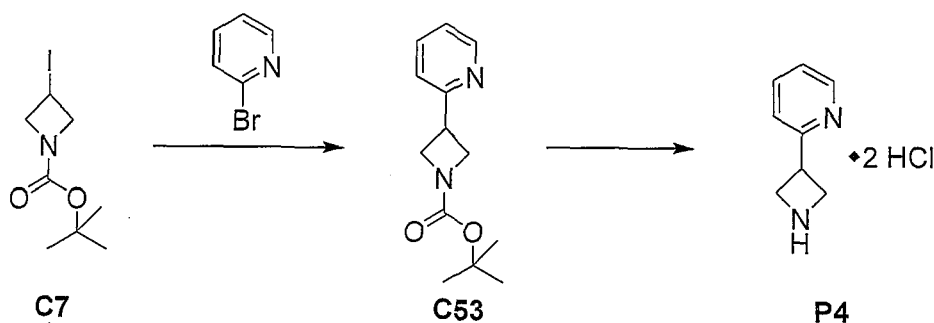
A. Preparation of 3-(3-fluorophenoxy)-1-(diphenylmethyl)azetidine (**C52**). Compound **C52** was prepared according to the procedure described for the synthesis of **C51** in Preparation 2, except that 3-fluorophenol was used in place of 3-chlorophenol. Yield: 9.5 g, 28.5 mmol, 85%. This material was  
5 used in the next step without additional purification.

B. Preparation of compound **P3**. To a stirred solution of **C52** (5 g, 15 mmol) in ethanol (50 mL) was added ammonium formate (4.2 g, 75 mmol) followed by addition of 10% palladium on carbon (1 g) and the resulting suspension was heated at reflux for 6 h. Catalyst was then removed by  
10 filtration through Celite and the solids were washed with EtOH. The combined filtrates were concentrated *in vacuo* to provide a residue, which was purified by silica gel chromatography (Eluant: EtOAc: hexane) to afford **P3** as its free base. This was converted to the hydrochloride salt by stirring in ethanolic hydrochloric acid at 0°C. After 1 h, the solvent was removed under reduced  
15 pressure, and the residue obtained was stirred and washed with diethyl ether to afford **P3** as an off-white solid. Yield: 1.5 g, 9.0 mmol, 50%. M.P. 104-106°C. MS *m/z* 168 (M+1). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.94 (br s, 2H), 4.42 (br s, 2H), 5.05-5.11 (m, 1H), 6.71-6.74 (dd, *J* = 2.2, 2.2 Hz, 1H), 6.76-6.80 (m, 1H), 6.82-6.87 (m, 1H), 7.32-7.37 (m, 1H), 9.61 (br s, 2H).

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#### Preparation 4

##### Preparation of 2-azetidin-3-ylpyridine dihydrochloride



A. Preparation of *tert*-butyl 3-pyridin-2-ylazetidine-1-carboxylate (**C53**). Compound **C53** was prepared according to the procedure described for the preparation of **C8** in Example 1, except that 2-bromopyridine was used in  
25 place of 2-bromo-4-methylpyridine. Yield: 15.7 g, 67 mmol, 67%. <sup>1</sup>H NMR

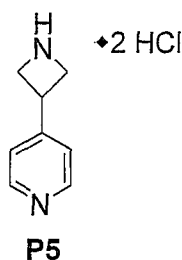
-70-

(400 MHz, DMSO- $d_6$ )  $\delta$  1.40 (s, 9H), 3.87–4.04 (m, 3H), 4.15–4.19 (m, 2H), 7.25–7.32 (m, 2H), 7.74 (dd,  $J=6, 6$  Hz, 1H), 8.59 (d,  $J=4$  Hz, 1H).

B. Preparation of compound **P4**. A solution of hydrochloric acid in dioxane (4M, 67 mL, 0.27 mol) was added to a solution of **C53** (15.7 g, 67 mmol) in MeOH (600 mL). The reaction mixture was stirred for 1 h at 40–50°C and then concentrated *in vacuo*. The residue was recrystallized from MeOH to afford **P4**. Yield: 11.2 g, 54.1 mmol, 80%. MS (APCI)  $m/z$  135.1 (M+1).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  4.26–4.31 (m, 4H), 4.48–4.57 (m, 1H), 7.77 (dd,  $J=7.1, 7.1$  Hz, 1H), 8.06 (d,  $J=7.1$  Hz, 1H), 8.36 (dd, 1H,  $J=7, 7.1$  Hz), 8.76 (d,  $J=7$  Hz, 1H), 9.57 (s, 1H), 9.89 (s, 1H).

#### Preparation 5

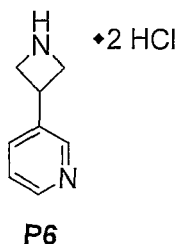
##### Preparation of 4-azetidin-3-ylpyridine dihydrochloride



Compound **P5** was prepared according to the general procedure described for the synthesis of **P4** in Preparation 4. The resulting precipitate was filtered off and recrystallized from a MeOH/THF mixture to provide the dihydrochloride **P5**. Yield: 6.6 g, 31.9 mmol, 68%. MS (APCI)  $m/z$  135.1 (M+1).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  4.1–4.2 (m, 2H), 4.27–4.45 (m, 3H), 8.1 (d,  $J=6.6$  Hz, 2H), 8.91 (d,  $J=6$  Hz, 2H), 9.66 (br s, 1H), 9.82 (br s, 1H).

#### Preparation 6

##### Preparation of 3-azetidin-3-ylpyridine dihydrochloride



Compound **P6** was prepared according to the general procedures described for the synthesis of **P4** in Preparation 4, to provide the



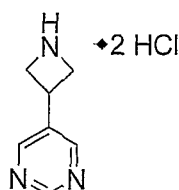
-71-

dihydrochloride **P6**. Yield: 8 g, 38.6 mmol, 53%. MS (APCI)  $m/z$  135.1 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  4.13-4.22 (m, 2H), 4.26-4.36 (m, 3H), 8.00 (dd,  $J=6.1, 6.1$  Hz, 1H), 8.65 (d,  $J=6.1$  Hz, 1H), 8.81 (d,  $J=6.1$  Hz, 1H), 9.01 (s, 1H), 9.52 (br s, 1H), 9.74 (br s, 1H).

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### Preparation 7

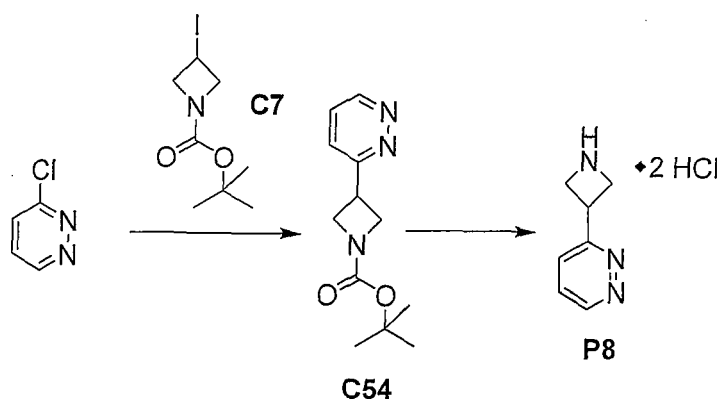
#### Preparation of 5-azetidin-3-ylpyrimidine dihydrochloride

**P7**

Compound **P7** was prepared according to the general procedures described for the synthesis of **P4** in Preparation 4, to provide the dihydrochloride **P7**. Yield: 5.2 g, 25 mmol, 39%.  $^1\text{H}$  NMR: (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  4.15-4.22 (m, 3H), 4.24-4.30 (m, 2H), 9.02 (s, 2H), 9.17 (s, 1H), 9.41-9.57 (s, 1H), 9.59-9.75 (s, 1H).

### Preparation 8

#### Preparation of 3-azetidin-3-ylpyridazine dihydrochloride



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A. Preparation of *tert*-butyl 3-pyridazine-3-ylazetidine-1-carboxylate (**C54**). Compound **C54** was prepared according to the procedure described in the synthesis of **C8** in Example 1, except that 3-chloropyridazine was used in place of 2-bromo-4-methylpyridine. Yield: 5 g, 18.5 mmol, 10%.

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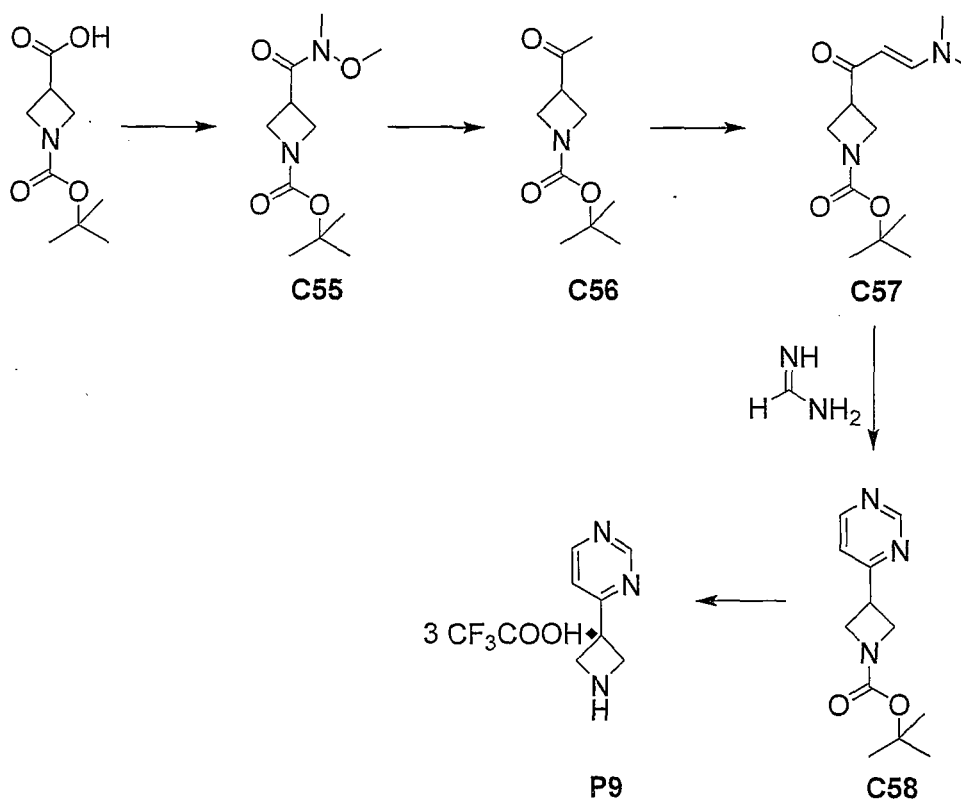
B. Preparation of compound **P8**. Compound **P8** was prepared according to the procedure described in the preparation of **P4**, except that

**C54** was used instead of **C53**. Yield: 3.7 g, 15.3 mmol, 54%.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  4.13–4.22 (m, 2H), 4.26–4.36 (m, 3H), 8.00 (dd,  $J=6$ , 6 Hz, 1H), 8.65 (d,  $J=6$  Hz, 1H), 8.81 (d,  $J=6$  Hz, 1H), 9.01 (s, 1H), 9.52 (br s, 1H), 9.74 (br s, 1H).

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### Preparation 9

#### Preparation of 4-azetidin-3-ylpyrimidine tris(trifluoroacetate)



A. Preparation of *tert*-butyl 3-[[methoxy(methyl)amino]carbonyl]azetidine-1-carboxylate (**C55**). To a solution of 1-(*tert*-butoxycarbonyl)azetidine-3-carboxylic acid (22.3 g, 0.111 mol) in THF (250 mL), 1,3-dicyclohexylcarbodiimide (24.4 g, 0.150 mol) was added portion-wise. The reaction mixture was stirred at room temperature for 1.5 h before addition of a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (15.0 g, 0.154 mol) in a mixture of acetonitrile (300 mL) and triethylamine (22.6 mL, 0.162 mol). The resulting mixture was stirred at room temperature for 24 h, and then the reaction was concentrated *in vacuo*. The residue was taken up in water (300 mL) and EtOAc (800 mL), the organic layer was separated, washed with a 5%

aqueous citric acid solution (2 × 200 mL), water (2 × 150 mL), and saturated aqueous sodium chloride solution (2 × 150 mL), and then dried over magnesium sulfate. Filtration and removal of solvent gave **C55** as a light yellow oil. Yield: 28.15 g, 0.12 mol, 100%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.12–4.09 (m, 2H), 4.03–3.99 (m, 2H), 3.64–3.56 (m, 1H), 3.63 (s, 3H), 3.17 (s, 3H), 1.40 (s, 9H).

B. Preparation of *tert*-butyl 3-acetylazetidine-1-carboxylate (**C56**). A solution of **C55** (27.1 g, 0.111 mol) in THF (200 mL) was added drop-wise to a 1.4M solution of methylmagnesium bromide in a mixture of THF and toluene (25:75) (99.0 mL, 0.139 mol) over 40 mins, while the reaction temp was kept at about 0°C. After completion of the addition, the mixture was stirred at 10–15°C for 2 hours, followed by 1 h at room temp. The reaction mixture was cooled to 0°C and quenched with a 10% aqueous citric acid solution (150 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 300 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (2 × 250 mL), and dried over sodium sulfate. Filtration and removal of solvent gave a residue, which was purified by silica gel chromatography (Eluant: chloroform) to afford **C56**. Yield: 20.6 g, 0.10 mol, 93%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 4.04–4.02 (m, 4H), 3.43–3.35 (m, 1H), 2.16 (s, 3H), 1.42 (s, 9H).

C. Preparation of *t*-butyl 3-[(2*E*)-3-(dimethylamino)prop-2-enoyl]azetidine-1-carboxylate (**C57**). A solution of **C56** (20.6 g, 0.103 mol) in DMF dimethyl acetal was heated at reflux for 45 h. The reaction mixture was evaporated and azeotroped with toluene (2 × 200 mL) to afford **C57**, which was used in the next step without additional purification. Yield: 28.0 g, 0.11 mol, >100%.

D. Preparation of *tert*-butyl 3-pyrimidin-4-ylazetidine-1-carboxylate (**C58**). Formamidine hydrochloride (4.96 g, 0.062 mol) and a solution of **C57** in MeOH (75 mL) were added in sequence to a solution of sodium methoxide (3.33 g, 0.062 mol) in MeOH (75 mL). The reaction mixture was heated at

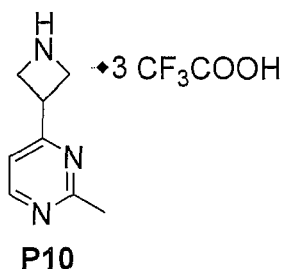
reflux for 50 h, the solvent was exchanged for dioxane and the mixture was heated at reflux for another 40 h. At that point, the solvent was removed *in vacuo*, and the residue treated with water (150 mL) and EtOAc (250 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 250 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Eluant: EtOAc) to afford **C58**. Yield: 2.0 g, 8.5 mmol, 21%. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.18 (d, *J*=1.2 Hz, 1H), 8.73 (d, *J*=5.1 Hz, 1H), 7.48 (dd, *J*=5.1, 1.2 Hz, 1H), 4.21–4.17 (m, 2H), 4.02–3.98 (m, 2H), 3.96–3.88 (m, 1H), 1.39 (s, 9H).

E. Preparation of compound **P9**. Trifluoroacetic acid (9.9 mL, 14.7 g, 0.13 mol) was added to a 0–5°C solution of **C58** (1.9 g, 8 mmol) in dichloromethane (10 mL). The reaction mixture was stirred under cooling for 30 mins followed by 1 h at room temperature. The solvent was removed under reduced pressure and the resulting residue was azeotroped with dichloromethane (5 × 50 mL), and MeOH (5 × 50 mL) to afford **P9** as a brown syrup. Yield: 2.42 g, 7.9 mmol, 99%. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.33 (br s, 1H), 9.00 (br s, 1H), 9.24 (d, *J*=1.2 Hz, 1H), 8.78 (d, *J*=5.1 Hz, 1H), 7.52 (dd, *J*=5.1, 1.2 Hz, 1H), 4.33–4.19 (m, 5H).

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#### Preparation 10

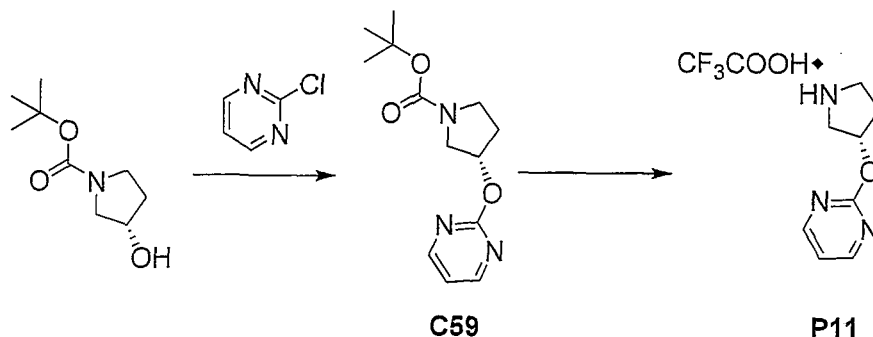
##### Preparation of 4-azetidin-3-yl-2-methylpyrimidine tris(trifluoroacetate)



Compound **P10** was prepared according to the general procedures described in Preparation 9, to provide **P10** as a white solid. Yield: 20.8 g, 42.2 mmol, 96%. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 15.29 (br s, 2H), 9.15 (br s, 1H), 8.83 (br s, 1H), 8.66 (d, *J*=5.1 Hz, 1H), 7.31 (d, *J*=5.1 Hz, 1H), 4.29–4.15 (m, 5H), 2.65 (s, 3H).

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## Preparation 11

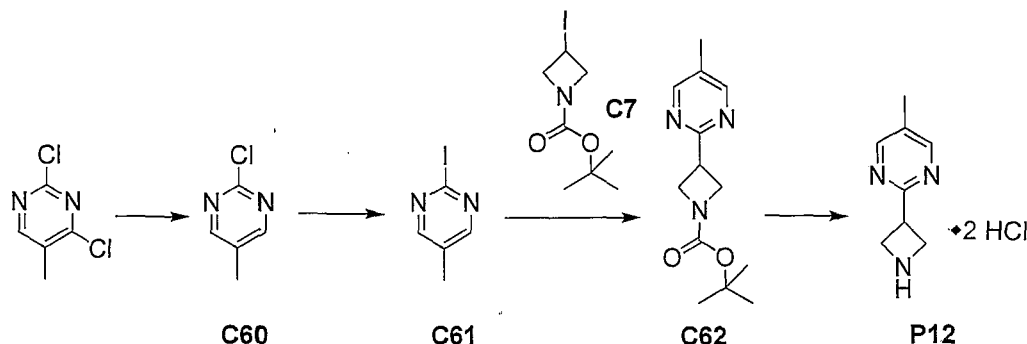
Preparation of 2-[(3*S*)-pyrrolidin-3-yloxy]pyrimidine trifluoroacetate

A. Preparation of *tert*-butyl (3*S*)-3-(pyrimidin-2-yloxy)pyrrolidine-1-carboxylate (**C59**). To a solution of *tert*-butyl (3*S*)-3-hydroxypyrrolidine-1-carboxylate (990 mg, 5.29 mmol) in THF (10 mL) was slowly added potassium *tert*-butoxide (593 mg, 5.29 mmol). The reaction mixture was stirred for 30 mins, and then 2-chloropyrimidine (606 mg, 5.29 mmol) was added. The mixture was stirred at room temperature and monitored by thin layer chromatography. The solvent was removed under reduced pressure, and the residue was treated with EtOAc and a saturated aqueous solution of sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Gradient: 0% to 100% EtOAc in hexane) to afford **C59**. Yield: 1.29 g, 4.9 mmol, 92%. LCMS *m/z* 266.3 (*M*+1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.43 (s, 9H), 2.10-2.25 (m, 2H), 3.50-3.64 (m, 4H), 5.51(m, 1H), 6.93 (m, 1H), 8.50 (m, 2H).

B. Preparation of compound **P11**. A mixture of **C59** (1.29 g, 4.85 mmol) and trifluoroacetic acid (5 mL) in dichloroethane (15 mL) was stirred at room temp for 4 hours. The solvent was removed *in vacuo* and the product was dried on high vacuum to give the trifluoroacetate salt **P11**, which was used in the next step without additional purification. LCMS *m/z* 166.2 (*M*+1). The (*R*)-enantiomer of **P11** can be prepared in the same way, using *tert*-butyl (3*R*)-3-hydroxypyrrolidine-1-carboxylate as starting material.

## Preparation 12

## Preparation of 2-azetidin-3-yl-5-methylpyrimidine dihydrochloride



A. Preparation of 2-chloro-5-methylpyrimidine (**C60**). A mixture of 2,4-dichloro-5-methylpyrimidine (50 g, 0.31 mol), water (500 mL) and zinc dust (50 g, 0.94 mol) was heated at reflux overnight. The reaction mixture was filtered and the filtrate was extracted with dichloromethane (3 x 500 mL). The organic layer was washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was recrystallized from petroleum ether to afford compound **C60** as a white solid. Yield: 27.9 g, 0.22 mol, 75%. LCMS *m/z* 129.3 (*M*+1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.25 (s, 3H), 8.40 (s, 2H).

B. Preparation of 2-iodo-5-methylpyrimidine (**C61**). Hydroiodic acid (13 mL), cooled to 0°C, was added to **C60** (2.0 g, 15.6 mmol) and the reaction mixture was stirred at 0°C for 1 h. The mixture was neutralized with a saturated aqueous solution of sodium bicarbonate and treated with sodium thiosulfate. The aqueous layer was extracted with EtOAc, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Gradient: 0% to 100% EtOAc in heptane) to afford **C61** as a white powder. Yield: 1.54 g, 6.99 mmol, 45%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.24 (s, 3H), 8.29 (s, 2H).

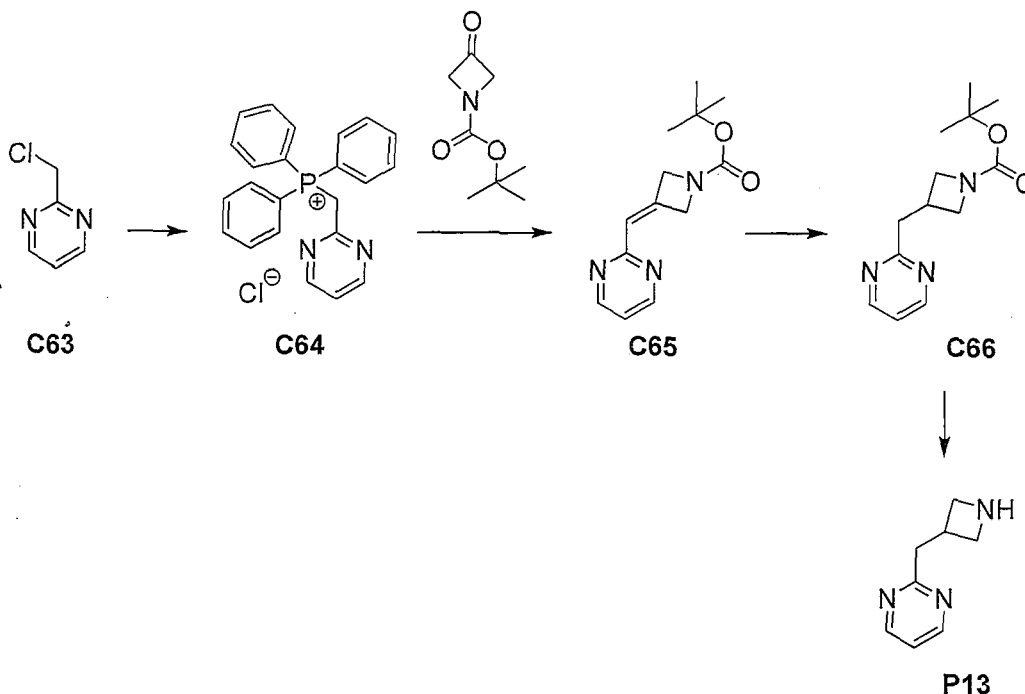
C. Preparation of *tert*-butyl 3-(5-methylpyrimidin-2-yl)azetidine-1-carboxylate (**C62**). Compound **C62** was prepared according to the procedure described for the synthesis of **C8** in Example 1, except that 2-iodo-5-methylpyrimidine **C61** was used in place of 2-bromo-4-methylpyridine. Yield:

1.01 g, 4.05 mmol, 81%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.44 (s, 9H), 2.37 (s, 3H), 4.25 (m, 3H), 4.33 (m, 2H), 8.78 (s, 2H).

D. Preparation of compound **P12**. To a solution of **C62** (469 mg, 1.88 mmol) in propan-2-ol was added a solution of hydrochloric acid in propan-2-ol (1N, 0.376 mL, 3.76 mmol) and the reaction mixture was stirred at room temperature for 18 h. The mixture was concentrated, the residue was diluted with dichloromethane and treated with an aqueous solution of sodium hydroxide (6N, 0.625 mL, 3.76 mmol). The organic layer was decanted, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting solid was triturated with a mixture of dichloromethane (1 mL) and diethyl ether (10 mL), filtered and washed with diethyl ether to afford **P12**. Yield: 203 mg, 1.36 mmol, 72%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.34 (s, 3H), 4.18-4.23 (m, 5H), 8.66 (s, 2H).

### Preparation 13

#### Preparation of 2-(azetidin-3-ylmethyl)pyrimidine



A. Preparation of 2-(chloromethyl)pyrimidine (**C63**) is described by M.G.N. Russel & R.W. Carling, *J. Med. Chem.*, 2005, 48, 1367-1383 and by Y. Todoroki & M. Sawada, *Bioorganic & Med. Chem.*, 2004, 13, 363-386.

B. Preparation of triphenyl(pyrimidin-2-ylmethyl)phosphonium chloride (**C64**). To a solution of **C63** (8 g, 48.5 mol) in benzene (80 mL) was added triphenylphosphine (12.7 g, 48.5 mol) and the mixture was heated at reflux for about 24 h. After the reaction mixture cooled to room temperature, the  
5 resulting solid was filtered and washed with benzene (80 mL). The filtrate was concentrated *in vacuo* to afford **C64**. Yield: 17.1 g, 48.2 mol, 99%. LCMS (ES<sup>+</sup>) *m/z* 355.2 (M<sup>+</sup>).

C. Preparation of *tert*-butyl 3-(pyrimidin-2-ylmethylene)azetidine-1-carboxylate (**C65**). A mixture of **C64** (900 mg, 2.3 mmol) and sodium *t*-  
10 butoxide (221 mg, 2.3 mmol) in dimethyl sulfoxide (20 mL) was stirred at room temperature for 1 h before *tert*-butyl 3-oxoazetidine-1-carboxylate (473 mg, 2.76 mmol) was added. The reaction mixture was stirred for about 18 h, diluted with dichloromethane (50 mL) and treated with water (25 mL). The mixture was stirred for 10 mins, and the organic layer was decanted, dried  
15 over magnesium sulfate, filtered and concentrated. The residue was pre-adsorbed on silica gel and purified by chromatography to afford **C65**. Yield: 460 mg, 1.86 mmol, 80%. LCMS (ES<sup>+</sup>) *m/z* 248.3 (M+1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.46 (s, 9H), 4.67 (s, 2H), 4.94 (m, 2H), 6.44 (br s, 1H), 7.03 (t, *J*=4.9 Hz, 1H), 8.65 (d, *J*=5.0 Hz, 2H).

20 D Preparation of *tert*-butyl 3-(pyrimidin-2-ylmethyl)azetidine-1-carboxylate (**C66**). To a mixture of piperidine (1.27 g, 14.9 mmol) and formic acid (1.59 mL, 14.9 mmol) in EtOH (50 mL) was added **C65** (3.5 g, 14.2 mmol) and palladium (10% weight on carbon, 350 mg). The reaction mixture was heated to 78°C for 5 h, filtered through a pad of Celite and concentrated  
25 *in vacuo*. The residue was pre-adsorbed on silica gel and purified by chromatography (Gradient: heptane: EtOAc) to afford **C66**. Yield: 3.23 g, 13.0 mmol, 92%. LCMS (ES<sup>+</sup>) *m/z* 250.4 (M+1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.41 (s, 9H), 3.09 (m, 1H), 3.24 (d, *J*=7.7 Hz, 2H), 3.72 (dd, *J*=8.8, 5.5 Hz, 2H), 4.07 (dd, *J*=8.5, 8.5 Hz, 2H), 7.13 (t, *J*=4.9 Hz, 1H), 8.63 (d, *J*=5 Hz, 2H).

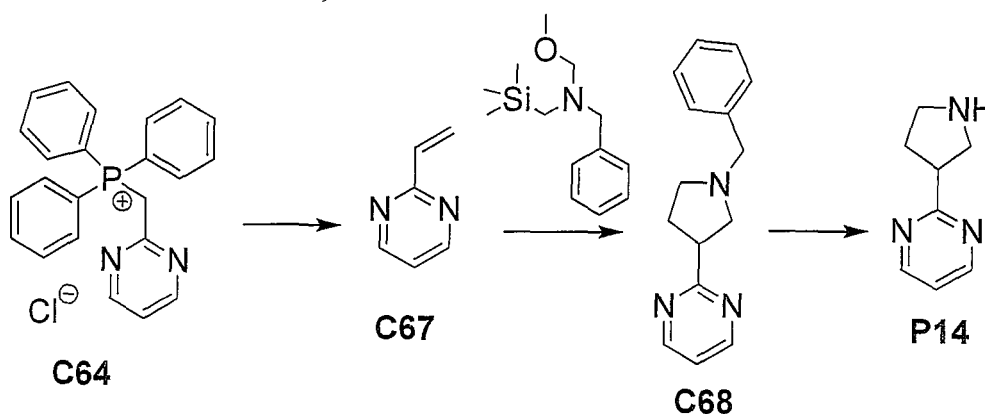
30 E. Preparation of compound **P13**. **P13** was prepared according to the procedure described for the synthesis of **P11** in Preparation 11, except that



**C66** was used in place of **C59**. Compound **P13** was used in the next step without additional purification.

#### Preparation 14

##### Preparation of 2-pyrrolidin-3-yl-pyrimidine



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10  
15  
A. Preparation of 2-vinylpyrimidine (**C67**). Sodium *tert*-butoxide (1.22 g, 12.7 mmol) was added to a solution of **C64** (4.5 g, 12.7 mmol) in THF (13 mL), and the reaction mixture was stirred at room temperature for 2 h. A solution of formaldehyde in water (37%, 2.8 mL, 38 mmol) was added and the mixture was stirred for an additional 18 h. The reaction mixture was pre-adsorbed on silica gel and purified twice by chromatography (Eluant: diethyl ether) to afford **C67**. Yield: 950 mg, 8.96 mmol, 71%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.72 (dd, *J*=10.6, 2.1 Hz, 1H), 6.60 (dd, *J*=17.4, 2.1 Hz, 1H), 6.86 (dd, *J*=17.4, 10.6 Hz, 1H), 7.11 (t, *J*=4.9 Hz, 1H), 8.68 (d, *J*=4.8 Hz, 2H).

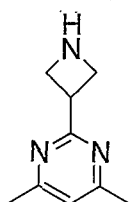
20  
B. Preparation of 2-(1-benzylpyrrolidin-3-yl)pyrimidine (**C68**). To a solution of **C67** (888 mg, 8.37 mmol) in dichloromethane (8 mL) was added trifluoroacetic acid (0.19 mL, 2.51 mmol), followed by drop-wise addition of a solution of N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine (2.58 g, 10.9 mmol) in dichloromethane (8 mL). The reaction mixture was stirred at room temperature for about 18 h. The reaction mixture was pre-adsorbed on silica gel and purified by chromatography (Gradient: dichloromethane: MeOH) to afford **C68**. Yield: 1.37 g, 5.73 mmol, 68%. LCMS (ES<sup>+</sup>) *m/z* 240.4 (M+1).

25  
C. Preparation of 2-pyrrolidin-3-yl-pyrimidine (**P14**). To a mixture of ammonium formate (166 mg, 2.51 mmol) in MeOH (8 mL) was added a

solution of **C68** (600 mg, 2.51 mmol) in EtOH (2 mL) and palladium on carbon (10%, 60 mg). The reaction was heated to 60°C for 46 h and then left for 24 h at room temperature. The reaction mixture was filtered through a pad of Celite, and the filtrate was pre-adsorbed on silica gel. Purification via silica gel chromatography (Gradient: heptane: EtOAc) gave **P14**. Yield: 120 mg, 0.80 mmol, 32%. This material was not pure, as assessed by <sup>1</sup>H NMR, but was used without additional purification.

### Preparation 15

#### Preparation of 2-azetidin-3-yl-4,6-dimethylpyrimidine

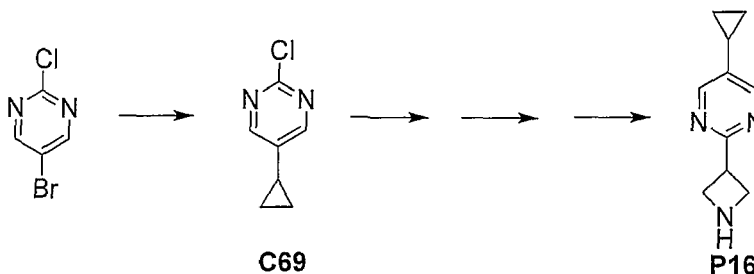


**P15**

Compound **P15** was prepared according to the general procedure described for the synthesis of **P12** in Preparation 12, except that 2-chloro-4,6-dimethylpyrimidine (the synthesis of 2-chloro-4,6-dimethylpyrimidine is described by G. Vlad & I.T. Horvath, *J. Organic Chem.*, 2002, 67, 6550-6552) was used instead of 2-chloro-5-methylpyrimidine, to provide **P15**. Yield: 345 mg, 2.11 mmol, 43%. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 2.44 (s, 6H), 4.00 (m, 2H), 4.14 (m, 3H), 7.12 (s, 1H).

### Preparation 16

#### Preparation of 2-azetidin-3-yl-5-cyclopropylpyrimidine



20

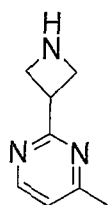
A. Preparation of 2-chloro-5-cyclopropylpyrimidine (**C69**). Compound **C69** was prepared from 5-bromo-2-chloropyrimidine according to the procedure described by D. J. Wallace & C-y. Chen; *Tetrahedron Letters*,

2002, 43, 6987-6990.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.79 (m, 2H), 1.14 (m, 2H), 1.87 (m, 1H), 8.36 (s, 2H).

B. Preparation of 2-azetidin-3-yl-5-cyclopropylpyrimidine (**P16**).  
Compound **P16** was prepared according to the general procedures described  
5 for the synthesis of **P12** in Preparation 12, except that 2-chloro-5-cyclopropylpyrimidine **C69** was used in place of 2-chloro-5-methylpyrimidine. Yield: 303 mg, 1.73 mmol, 59%.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  0.82 (m, 2H), 1.10 (m, 2H), 1.96 (m, 1H), 4.2-4.3 (br m, 5H), 8.55 (s, 2H).

#### Preparation 17

10 Preparation of 2-azetidin-3-yl-4-methylpyrimidine

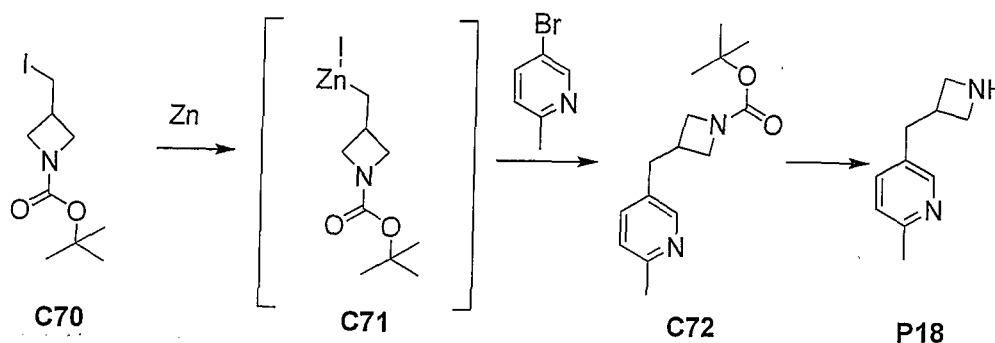


**P17**

Compound **P17** was prepared according to the general procedure for  
the synthesis of **P12** described in Preparation 51, except that 2-chloro-4-methylpyrimidine (the synthesis of 2-chloro-4-methylpyrimidine is described  
15 by D.B. Harden & M.J. Mokrosz, *J. Organic Chem.*, 1998, 53, 4137-4140) was used instead of 2-chloro-5-methylpyrimidine, to provide **P17**. Yield: 647 mg, 4.34 mmol, 87%.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  2.52 (s, 3H), 4.0 (m, 2H), 4.12 (m, 2H), 4.18 (m, 1H), 7.23 (d,  $J=5.4$  Hz, 1H), 8.59 (d,  $J=5.4$  Hz, 1H).

#### Preparation 18

20 Preparation of 5-(azetidin-3-ylmethyl)-2-methylpyridine



A. *tert*-Butyl-3-(iodomethyl)azetidine-1-carboxylate (**C70**) was prepared according to the procedure described by W.A. Slusarchyk & S.A. Bolton, *Bioorganic & Med. Chem. Letters*, 2002, 12, 3235-3238.

B. Preparation of {[1-(*t*-butoxycarbonyl)azetidin-3-yl]methyl}(iodo)zinc (**C71**). Zinc powder (116.5 g, 1.78 mol) was suspended in dimethylacetamide (300 mL) under argon. A mixture of trimethylsilyl chloride and 1,2-dibromoethane (7:5 v/v, 34.5 mL) was added and the mixture was stirred for 20 mins. A solution of **C70** (426.8 g, 1.437 mol) in dimethylacetamide (650 mL) was added under water cooling and the reaction mixture was stirred overnight. The concentration of the resulting solution of compound **C71** was about 1 mol/L and this was used in the next step.

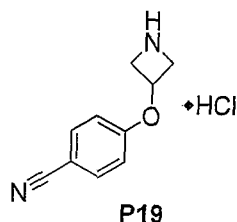
C. Preparation of *t*-butyl 3-[(6-methylpyridin-3-yl)methyl]azetidine-1-carboxylate (**C72**). 5-Bromo-2-methylpyridine (25 g, 0.145 mol) was dissolved in dimethylacetamide (150 mL) and the solution was degassed. To the solution was added tetrakis(triphenylphosphine)palladium(0) (5 g, 4.4 mmol), copper iodide (1.7 g, 8.7 mmol) and the 1 mol/L solution of compound **C71** (170 mL) under an atmosphere of argon. The reaction mixture was stirred at 50°C for 12 h; during this time, partial decomposition of the catalyst was observed and additional amounts of tetrakis(triphenylphosphine)palladium(0) (5 g, 4.4 mmol) and copper iodide (0.9 g, 4.7 mmol) were added. The reaction mixture was stirred at 50°C for 48 h, cooled and poured into a mixture of a saturated aqueous solution of ammonium chloride (600 mL) and diethyl ether (600 mL). The resulting mixture was stirred for 30 mins and filtered through a layer of Celite to remove insoluble impurities. The organic layer was separated and the aqueous layer was extracted with diethyl ether (4 × 300 mL). The combined organic extracts were dried over anhydrous sodium sulfate and evaporated. The residue was purified by silica gel chromatography (Eluant: EtOAc) to afford compound **C72**. Yield: 27.9 g, 0.106 mol, 73%.

D. Preparation of compound **P18**. Compound **C72** (27.9 g, 0.106 mol) was dissolved in trifluoroacetic acid (100 mL) at 0°C and the reaction mixture was stirred at this temperature for 2 h before evaporation. The residue was

azeotroped with benzene, the resulting trifluoroacetate salt was treated with a 30% solution of potassium carbonate and the free base product was extracted with dichloromethane several times. The combined organic extracts were evaporated and purified by silica gel chromatography (Eluant: chloroform: MeOH: ammonia) to give compound **P18**. Yield: 3.8 g, 0.024 mol, 23%. LCMS  $m/z$  163.1 (M+1).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  2.40 (s, 3H), 2.79 (m, 3H), 2.93 (m, 1H), 3.23 (m, 2H), 3.44 (m, 2H), 7.12 (d, 1H), 7.45 (dd, 1H), 8.26 (d, 1H).

#### Preparation 19

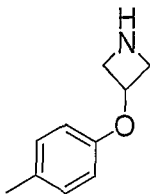
##### 10 Preparation of 4-(azetidin-3-yloxy)benzonitrile hydrochloride



Compound **P19** was prepared according to the general procedures described for the synthesis of **C50** in Preparation 1, except that 4-hydroxybenzonitrile was used instead of 4-(trifluoromethyl)phenol. The final deprotection step was as described in the preparation of **P2** in Preparation 2, affording **P19** as a white solid. Yield: 34.9 g, 0.166 mmol, 71%. Melting point 88-90°C.

#### Preparation 20

##### Preparation of 3-(4-methylphenoxy)azetidine



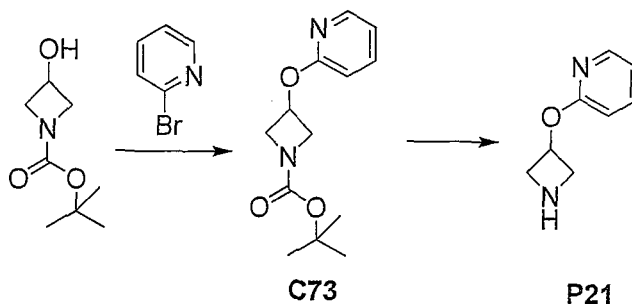
**P20**

Compound **P20** was prepared according to the general procedures described for the synthesis of **P1** in Preparation 1, except that 4-methylphenol was used instead of 4-(trifluoromethyl)phenol, to afford **P20** as a yellow oil. Yield: 3.6 g, 0.02 mol, 69%. LCMS  $m/z$  164.1 (M+1).  $^1\text{H}$  NMR (400 MHz,

DMSO- $d_6$ )  $\delta$  2.24 (s, 3H), 3.48 (m, 2H), 3.72 (m, 2H), 4.89 (m, 1H), 6.67 (d, 2H), 7.06 (d, 2H).

### Preparation 21

#### Preparation of 2-(azetidin-3-yloxy)pyridine

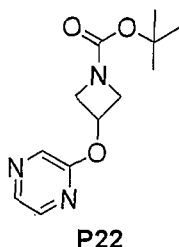


- 5 A. Preparation of *t*-butyl 3-(pyridin-2-yloxy)azetidine-1-carboxylate (**C73**). Compound **C73** was prepared from *tert*-butyl 3-hydroxyazetidine-1-carboxylate according to the procedure for the final step described in the preparation of Example 3, to afford **C73**. Yield: 578 mg, 2.31 mmol, 80%.
- 10 LCMS (ESI)  $m/z$  251.4 ( $M+1$ )  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.43 (s, 9H), 3.96 (m, 2H), 4.30 (m, 2H), 5.30 (m, 1H), 6.75 (m, 1H), 6.87 (m, 1H), 7.57 (m, 1H), 8.08 (m, 1H).

- B. Preparation of compound **P21**. Compound **P21** was prepared by deprotection of **C73** with trifluoroacetic acid as described for *t*-butyl 3-hydroxyazetidine-1-carboxylate in the preparation of **C19** in Example 3, before
- 15 being used in the coupling step.

### Preparation 22

#### Preparation of *tert*-butyl 3-(pyrazin-2-yloxy)azetidine-1-carboxylate



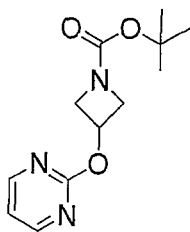
- 20 Compound **P22** was prepared according to the general procedure described for the synthesis of **P21** in Preparation 21, using 2-chloropyrazine in place of 2-bromopyridine, to afford **P22**. LCMS (ESI)  $m/z$  252.4 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.43 (s, 9H), 3.97 (m, 2H), 4.32 (m, 2H), 5.30

(m, 1H), 8.03 (dd,  $J=2.5, 1.2$  Hz, 1H), 8.16 (d,  $J=2.5$  Hz, 1H), 8.26 (d,  $J=1.2$  Hz, 1H). Compound **P22** was deprotected with trifluoroacetic acid as described for *tert*-butyl 3-hydroxyazetidine-1-carboxylate in the preparation of **C19** in Example 3, before being used in the coupling step.

5

#### Preparation 23

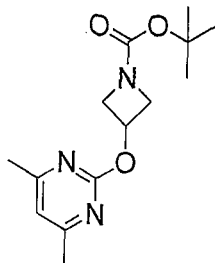
##### Preparation of *tert*-butyl 3-(pyrimidin-2-yloxy)azetidine-1-carboxylate

**P23**

Compound **P23** was prepared according to the general procedure described in the preparation of **P21** in Preparation 21, except that 2-chloropyrimidine was employed instead of 2-bromopyridine, to afford **P23**.  
10  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.42 (s, 9H), 4.02 (m, 2H), 4.30 (m, 2H), 5.29 (m, 1H), 6.97 (t,  $J=4.9$  Hz, 1H), 8.50 (d,  $J=4.9$  Hz, 2H). Compound **P23** was deprotected with trifluoroacetic acid as described for *t*-butyl 3-hydroxyazetidine-1-carboxylate in the preparation of **C19** in Example 3, before  
15 being used in the coupling step.

#### Preparation 24

##### Preparation of *tert*-butyl 3-[(4,6-dimethylpyrimidin-2-yl)oxy]azetidine-1-carboxylate

**P24**

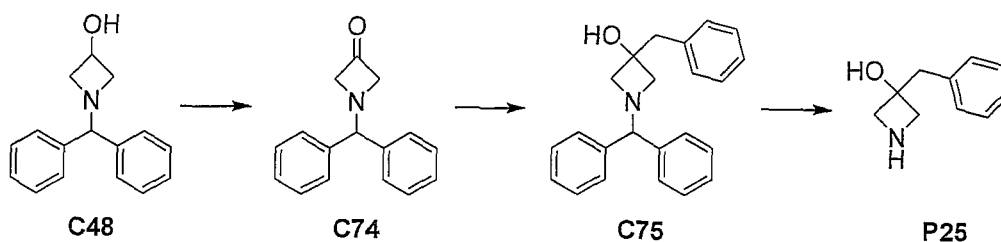
20 Compound **P24** was prepared according to the general procedure described in the preparation of **P21**, except that 2-chloro-4,6-dimethylpyrimidine was used in place of 2-bromopyridine, to afford **P24**. LCMS (ESI)  $m/z$  280.3 ( $M+1$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.39 (s, 9H), 2.34

(s, 6H), 3.96 (m, 2H), 4.25 (m, 2H), 5.26 (m, 1H), 6.66 (s, 1H). Compound **P24** was deprotected with trifluoroacetic acid as described for *tert*-butyl 3-hydroxyazetidine-1-carboxylate in the preparation of **C19**, Example 3 before being used in the coupling step.

5

### Preparation 25

#### Preparation of 3-benzylazetidin-3-ol



A. Preparation of 1-(diphenylmethyl)azetidin-3-one (**C74**). To a solution of pyridine sulfur trioxide (29.95 g, 188 mmol) in DMSO (100 mL) at 0°C, was added triethylamine (26.2 mL) and **C48** (15.0 g, 62.7 mmol) in DMSO (50 mL). The mixture was warmed to room temperature after 5 mins and stirred for 3 h. The reaction was quenched with saturated aqueous sodium chloride solution and extracted with EtOH; the organic layer was washed with a saturated aqueous solution of sodium bicarbonate, saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography (Eluant: 1:1:100:200 MeOH: triethylamine: EtOAc: hexane) to afford **C74** as a yellow solid. Yield: 12.2 g, 51.4 mmol, 82%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.02 (s, 4H), 4.61 (s, 1H), 7.23 (m, 2H), 7.32 (m, 4H), 7.49 (m, 4H).

B. Preparation of 3-benzyl-1-(diphenylmethyl)azetidin-3-ol (**C75**). To a solution of **C74** (5.8 g, 24.4 mmol) in anhydrous diethyl ether (200 mL) at –78°C was added benzylmagnesium chloride (1.0M, 24.4 mL, 24.4 mmol). The mixture was gradually warmed to room temperature and stirred overnight. The mixture was cooled to 0°C, quenched with water and filtered through Celite. The filtrate was extracted with EtOAc, and the organic extract was washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and evaporated. The residue was purified by silica gel

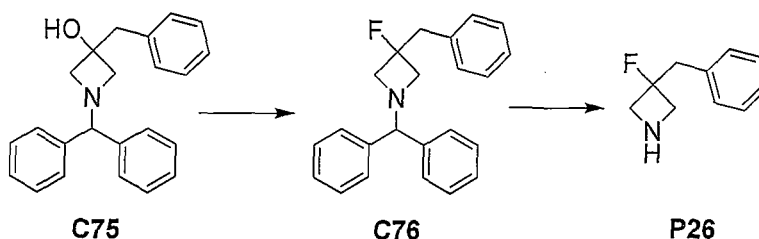


chromatography (Eluant: 1:9 EtOAc: hexane) to afford **C75** as a white solid. Yield: 3.0 g, 9.1 mmol, 37%.

- C. Preparation of 3-benzylazetidin-3-ol (**P25**). Compound **P25** was prepared according to the procedure described in the preparation of **P1** in Preparation 1, except that **C75** was used instead of **C50**. MS  $m/z$  164.1 (M+1).

#### Preparation 26

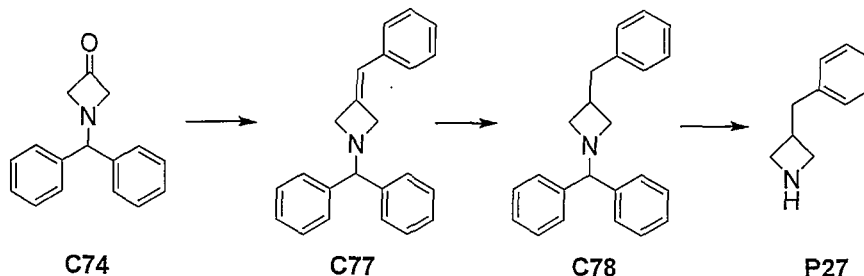
##### Preparation of 3-benzyl-3-fluoroazetidine



- A. Preparation of 3-benzyl-1-(diphenylmethyl)-3-fluoroazetidine (**C76**).

To a solution of **C75** (0.64 g, 1.95 mmol) in dry THF (20 mL) at  $-78^{\circ}\text{C}$ , was added (diethylamino)sulfur trifluoride (0.51 mL, 3.89 mmol). The mixture was slowly warmed to room temperature and stirred for 2 h. The reaction was diluted with EtOAc, washed with a saturated aqueous solution of sodium bicarbonate, then with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography (Eluant: 1:9 EtOAc: hexane) to afford **C76** as a yellow oil. Yield: 0.52 g, 1.57 mmol, 81%. MS  $m/z$  332.1 (M+1).

- B. Preparation of 3-benzyl-3-fluoroazetidine (**P26**). Compound **P26** was prepared according to the procedure described in the preparation of **P1** in Preparation 1, except that **C76** was used instead of **C50**, to afford **P26**. Compound **P26** was used in the next step without further purification. MS  $m/z$  166.2 (M+1).

Preparation 27Preparation of 3-benzylazetidine

A. Preparation of 3-benzylidene-1-(diphenylmethyl)azetidine (**C77**). To a suspension of benzyl triphenylphosphonium bromide (7.31 g, 16.86 mmol) in anhydrous dimethyl sulfoxide, was added potassium *tert*-butoxide (2.08 g, 18.54 mmol). The mixture was stirred at room temperature for 10 mins before **C74** (2.0 g, 8.43 mmol) was added. The reaction mixture was heated to 60°C overnight, quenched with ice water and extracted with diethyl ether (4 x 300 mL). The combined organic extracts were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and evaporated. The residue was dissolved in hot hexane (100 mL) and cooled to room temperature. The resulting solid was removed by filtration, and the filtrate was evaporated to afford **C77** as a yellow solid. Yield: 2.8 g, 8.93 mmol, quantitative. MS *m/z* 312.3 (*M*+1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.96 (m, 2H), 4.14 (m, 2H), 4.60 (m, 1H), 6.18 (s, 1H), 7.05 (m, 2H), 7.20-7.35 (m, 9H), 7.47 (m, 4H).

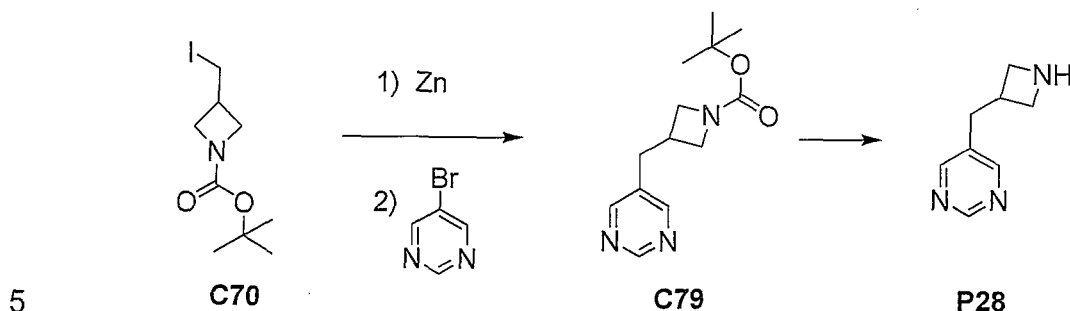
B. Preparation of 3-benzyl-1-(diphenylmethyl)azetidine (**C78**). To a solution of **C77** (0.85 g, 2.74 mmol) in MeOH (20 mL) and hexane (20 mL), was added palladium on carbon (10% wet, 200 mg). The reaction mixture was hydrogenated in a Parr apparatus for 6 hours at room temperature under 40 psi of hydrogen. The mixture was filtered and concentrated *in vacuo* to afford **C78**, which was used in the next step without additional purification.

C. Preparation of 3-benzylazetidine (**P27**). Compound **P27** was prepared according to the procedure described in the preparation of **P1** in Preparation 1, except that **C78** was used in place of **C50**, to afford **P27**.

Compound **P27** was used in the next step without additional purification. MS  $m/z$  148.2 ( $M+1$ ).

### Preparation 28

#### Preparation of 5-(azetidin-3-ylmethyl)pyrimidine

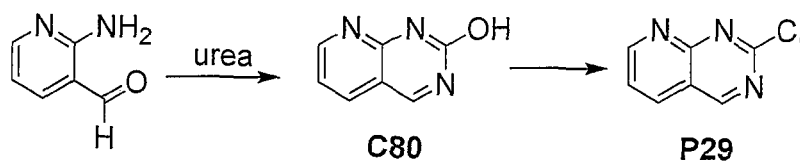


A. Preparation of *tert*-butyl 3-(pyrimidin-5-ylmethyl)azetidine-1-carboxylate (**C79**). Compound **C79** was prepared according to the general method for the synthesis of **C72** in Preparation 18, except that 5-bromopyrimidine was used instead of 5-bromo-2-methylpyridine. Yield: 51.5 g, 0.206 mol, 83%.

B. Preparation of 5-(azetidin-3-ylmethyl)pyrimidine (**P28**). A solution of **C79** (51.5 g, 0.026 mol) in MeOH (100 mL) was treated with a solution of hydrochloric acid in dioxane (4M, 250 mL), and the mixture was stirred for 18 h. Solvents were removed *in vacuo*, and the residue was re-evaporated with MeOH. The residue was purified twice via silica gel chromatography (Eluant: chloroform: MeOH: ammonia) to provide **P28**. Yield: 3.2 g, 0.021 mol, 10%.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  2.9 (m, 3H), 3.2 (m, 2H), 3.4 (m, 2H), 8.7 (s, 2H), 9.0 (s, 1H).

### Preparation 29

#### Preparation of 2-chloropyrido[2,3-*d*]pyrimidine



A. Preparation of pyrido[2,3-*d*]pyrimidin-2-ol (**C80**). A mixture of 2-aminonicotinaldehyde (100 g, 0.82 mol) and urea (220 g, 3.67 mol) was heated to 165°C for 4 h. When the oil bath had cooled to 90°C, water (350

mL) was added, and the reaction was left to cool further over about 18 h. The mixture was then filtered, and the solid was suspended in water (1 L) and placed in an ultrasonic bath for 1 h. This process was repeated twice, once with water and then with MeOH, to afford **C80** as a white solid, which was used in the next step without additional purification. Yield: 145 g >100%.

B. Preparation of 2-chloropyrido[2,3-*d*]pyrimidine (**P29**). A mixture of phosphorus oxychloride (750 mL) and **C80** (145 g,  $\leq 0.82$  mol, from the previous step) were heated at reflux for 4 h. After cooling to room temperature, the phosphorus oxychloride was removed under reduced pressure and the resulting oil and solid were diluted with cold dichloromethane and poured onto ice. This mixture was neutralized with a saturated aqueous sodium bicarbonate solution and filtered through Celite. Extraction of the filtrate with dichloromethane (5 x 1.5 L) was followed by combination of the organic extracts, which were dried over sodium sulfate, filtered and concentrated *in vacuo* to provide **P29** as an orange solid, which was used without additional purification. Yield: 30 g, 0.18 mol, 22% over two steps. LCMS  $m/z$  165.9 (M+1).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.6 (m, 1H), 8.4 (m, 1H), 9.3 (m, 1H), 9.4 (s, 1H).

Table 2

| Ex. No. | Prep'n Method  | Side Chain* | IUPAC Name   | MS<br>m/z<br>(M+1) | <sup>13</sup> C NMR (100 MHz), CDCl <sub>3</sub> (unless otherwise indicated),<br>observed peaks, δ (ppm); additional data                            |
|---------|--|-------------|--|--------------------|---|
| 14      | Ex. 4;<br>final purification<br>eluant 1:2:1%<br>EtOAc: hexanes:<br>NH <sub>4</sub> OH | com'l       | 1-cyclopentyl-6-[(1R)-1-[(3R)-3-phenylpyrrolidin-1-yl]propyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one          | 392.2,<br>APCI     | 9.81, 24.71, 32.33, 32.44, 32.71, 42.81, 43.17, 52.00, 52.70, 57.92, 105.10, 126.42, 126.54, 127.10, 128.56, 134.50, 158.01                           |
| 15      | Ex. 14   | com'l       | 1-cyclopentyl-6-[(1R)-1-[(3R)-3-phenylpyrrolidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one           | 378.2,<br>APCI     | 18.47, 18.63, 24.72, 32.41, 32.60, 32.77, 43.02, 43.29, 51.38, 52.31, 57.74, 105.02, 126.41, 126.50, 127.08, 128.55, 134.53, 158.02                   |
| 16      | Ex. 4;<br>final purification<br>eluant 1:1:1%<br>EtOAc: hexanes:<br>NH <sub>4</sub> OH | P1          | 1-cyclopentyl-6-(1-{3-[4-(trifluoromethyl)phenoxy]azetidin-1-yl}ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 447.9,<br>APCI     | 17.98, 24.71, 32.39, 32.42, 57.77, 58.53, 60.06, 65.19, 65.90, 105.04, 114.58, 127.11, 134.54, 151.92, 157.96, 159.13, 159.55                         |
| 17      | Ex. 16   | P2          | 6-[1-[3-(3-chlorophenoxy)azetidin-1-yl]ethyl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one            | 413.9,<br>APCI     | 18.02, 24.71, 32.38, 32.44, 57.77, 58.59, 60.18, 65.23, 65.87, 105.05, 112.98, 115.06, 121.67, 130.43, 134.56, 135.05, 151.93, 157.41, 157.92, 159.65 |

| Ex. No. | Prep'n Method  | Side Chain* | IUPAC Name  | MS<br>m/z<br>(M+1) | <sup>13</sup> C NMR (100 MHz), CDCl <sub>3</sub> (unless otherwise indicated),<br>observed peaks, δ (ppm); additional data   |
|---------|--|-------------|---|--------------------|--|
| 18      | Ex. 1;<br>final purification<br>gradient 0-10%<br>EtOH/EtOAc | P4          | 1-cyclopentyl-6-[(1R)-1-(3-pyridin-2-ylazetidin-1-yl)ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 365.2,<br>APCI     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.34 (d, J=6.8 Hz, 3H), 1.73 (m, 2H), 1.98 (m, 2H), 2.11 (m, 4H), 3.47 (dd, J=6.8, 6.8 Hz, 1H), 3.59 (q, J=6.8 Hz, 1H), 3.64 (dd, J=7.0, 7.0 Hz, 1H), 3.77 (m, 2H), 3.86 (m, 1H), 5.17 (m, 1H), 7.18 (br dd, J=7.6, 4.9 Hz, 1H), 7.23 (br d, J=8.3 Hz, 1H), 7.65 (ddd, J=7.7, 7.7, 1.9 Hz, 1H), 8.07 (s, 1H), 8.61 (br d, J=5.0 Hz, 1H) |
| 19      | Ex. 18   | P5          | 1-cyclopentyl-6-[(1R)-1-(3-pyridin-4-ylazetidin-1-yl)ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 365.2,<br>APCI     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.34 (d, J=6.8 Hz, 3H), 1.73 (m, 2H), 1.99 (m, 2H), 2.12 (m, 4H), 3.29 (dd, J=6.6, 6.6 Hz, 1H), 3.38 (dd, J=6.6, 6.6 Hz, 1H), 3.51 (q, J=6.8 Hz, 1H), 3.73 (m, 1H), 3.80 (m, 2H), 5.17 (m, 1H), 7.22 (m, 2H), 8.07 (s, 1H), 8.58 (m, 2H), 9.65 (br s, 1H)   |
| 20      | Ex. 18   | P6          | 1-cyclopentyl-6-[(1R)-1-(3-pyridin-3-ylazetidin-1-yl)ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 365.2,<br>APCI     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.35 (d, J=6.8 Hz, 3H), 1.73 (m, 2H), 1.99 (m, 2H), 2.12 (m, 4H), 3.29 (m, 1H), 3.38 (m, 1H), 3.52 (q, J=6.7 Hz, 1H), 3.73-3.84 (m, 3H), 5.17 (m, 1H), 7.31 (ddd, J=7.9, 4.8, 0.8 Hz, 1H), 7.70 (br ddd, J=7.9, 1.9, 1.9 Hz, 1H), 8.07 (s, 1H), 8.53 (m, 2H)  |

| Ex. No. | Prep'n Method  | Side Chain* | IUPAC Name  | MS<br>m/z<br>(M+1) | <sup>13</sup> C NMR (100 MHz), CDCl <sub>3</sub> (unless otherwise indicated),<br>observed peaks, δ (ppm); additional data  |
|---------|--|-------------|---|--------------------|---|
| 21      | Ex. 18   | P7          | 1-cyclopentyl-6-[(1R)-1-(3-pyrimidin-5-ylazetidin-1-yl)ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one         | 366.2,<br>APCI     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.36 (d, J=6.6 Hz, 3H), 1.73 (m, partially obscured by water, assumed 2H), 1.98 (m, 2H), 2.12 (m, 4H), 3.34 (dd, J=7.0, 7.0 Hz, 1H), 3.41 (dd, J=6.8, 6.8 Hz, 1H), 3.54 (q, J=6.7 Hz, 1H), 3.75 (m, 1H), 3.84 (m, 2H), 5.17 (m, 1H), 8.07 (s, 1H), 8.74 (s, 2H), 9.15 (s, 1H), 9.65 (br s, 1H) |
| 22      | Ex. 18   | P8          | 1-cyclopentyl-6-[(1R)-1-(3-pyridazin-3-ylazetidin-1-yl)ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one         | 366.2,<br>APCI     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.36 (d, J=6.6 Hz, 3H), 1.74 (m, 2H), 1.98 (m, 2H), 2.12 (m, 4H), 3.60 (dd, J=7.1, 7.1 Hz, 1H), 3.62 (q, J=6.7 Hz, 1H), 3.77 (dd, J=7.2, 7.2 Hz, 1H), 3.85 (m, 2H), 4.03 (m, 1H), 5.18 (m, 1H), 7.48 (m, 2H), 8.07 (s, 1H), 9.14 (dd, J=3.5, 3.1 Hz, 1H), 9.73 (br s, 1H)                      |
| 23      | Ex. 1;<br>final purification<br>gradient<br>MeOH/CH <sub>2</sub> Cl <sub>2</sub> | P28         | 1-cyclopentyl-6-[(1R)-1-[3-(pyrimidin-5-ylmethyl)azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 380.2,<br>LCMS     | 18.02, 24.67, 30.64, 32.39, 34.42, 57.52, 57.71, 57.89, 65.43, 105.03, 132.75, 134.50, 151.95, 156.51, 157.17   |
| 24      | Ex. 18   | P9          | 1-cyclopentyl-6-[(1R)-1-(3-pyrimidin-4-ylazetidin-1-yl)ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one         | 366.1,<br>APCI     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.34 (d, J=6.6 Hz, 3H), 1.72 (m, 2H), 1.97 (m, 2H), 2.10 (m, 4H), 3.48 (m, 1H), 3.56-3.65 (m, 2H), 3.74-3.85 (m, 3H), 5.16 (m, 1H), 7.26 (d, J=5.2 Hz, 1H), 8.05 (s, 1H), 8.67 (d, J=5.2 Hz, 1H), 9.21 (s, 1H), 9.82 (br s, 1H)  |

| Ex. No. | Prep'n Method | Side Chain*        | IUPAC Name   | MS<br><i>m/z</i><br>(M+1) | <sup>13</sup> C NMR (100 MHz), CDCl <sub>3</sub> (unless otherwise indicated),<br>observed peaks, $\delta$ (ppm); additional data  |
|---------|---------------|--------------------|--|---------------------------|--|
| 25      | Ex. 18        | C34<br>(see Ex. 6) | 6-[(1R)-1-(3-pyrimidin-2-ylazetidin-1-yl)ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 382.2,<br>APCI            | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.34 (d, J=6.6 Hz, 3H), 1.92 (m, 2H), 2.39 (m, 2H), 3.56-3.66 (m, 4H), 3.73 (dd, J=7.4, 7.4 Hz, 1H), 3.80 (dd, J=7.8, 7.8 Hz, 2H), 4.02 (m, 1H), 4.15 (m, 2H), 4.84 (m, 1H), 7.21 (t, J=4.8 Hz, 1H), 8.07 (s, 1H), 8.74 (d, J=4.8 Hz, 2H)   |
| 26      | Ex. 18        | P4                 | 6-[(1R)-1-(3-pyridin-2-ylazetidin-1-yl)ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one   | 381.2,<br>APCI            | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.34 (d, J=6.6 Hz, 3H), 1.92 (m, 2H), 2.38 (m, 2H), 3.47 (dd, J=6.9, 6.9 Hz, 1H), 3.57-3.66 (m, 4H), 3.77 (m, 2H), 3.87 (m, 1H), 4.15 (m, 2H), 4.84 (tt, J=11.8, 4.2 Hz, 1H), 7.18 (ddd, J=7.5, 5.0, 1.2 Hz, 1H), 7.23 (br d, J=7.9 Hz, 1H), 7.65 (ddd, J=7.7, 7.7, 1.9 Hz, 1H), 8.07 (s, 1H), 8.61 (ddd, J=5.0, 1.9, 0.9 Hz, 1H) |
| 27      | Ex. 18        | P5                 | 6-[(1R)-1-(3-pyridin-4-ylazetidin-1-yl)ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one   | 381.2,<br>APCI            | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.34 (d, J=6.8 Hz, 3H), 1.92 (m, 2H), 2.39 (m, 2H), 3.28 (dd, J=6.7, 6.7 Hz, 1H), 3.39 (dd, J=6.6, 6.6 Hz, 1H), 3.51 (q, J=6.8 Hz, 1H), 3.62 (m, 2H), 3.74 (m, 1H), 3.81 (m, 2H), 4.16 (m, 2H), 4.84 (m, 1H), 7.22 (m, 2H), 8.08 (s, 1H), 8.58 (m, 2H), 9.69 (br s, 1H)   |
| 28      | Ex. 18        | P6                 | 6-[(1R)-1-(3-pyridin-3-ylazetidin-1-yl)ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one   | 381.2,<br>APCI            | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.35 (d, J=6.8 Hz, 3H), 1.93 (m, 2H), 2.39 (m, 2H), 3.29 (m, 1H), 3.39 (m, 1H), 3.53 (q, J=6.7 Hz, 1H), 3.62 (m, 2H), 3.72-3.84 (m, 3H), 4.16 (m, 2H), 4.84 (m, 1H), 7.31 (ddd, J=7.9, 5.0, 0.8 Hz, 1H), 7.69 (ddd, J=8.1, 1.9, 1.9 Hz, 1H), 8.08 (s, 1H), 8.52-8.54 (m, 2H), 9.71 (br s, 1H)                                     |



| Ex. No. | Prep'n Method  | Side Chain* | IUPAC Name   | MS<br>m/z<br>(M+1) | <sup>13</sup> C NMR (100 MHz), CDCl <sub>3</sub> (unless otherwise indicated),<br>observed peaks, δ (ppm); additional data  |
|---------|--|-------------|--|--------------------|---|
| 29      | Ex. 18   | P7          | 6-[(1R)-1-(3-pyrimidin-5-ylazetidin-1-yl)ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one           | 382.2,<br>APCI     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.36 (d, J=6.6 Hz, 3H), 1.92 (m, 2H), 2.39 (m, 2H), 3.34 (dd, J=7.0, 7.0 Hz, 1H), 3.41 (dd, J=6.9, 6.9 Hz, 1H), 3.54 (q, J=6.7 Hz, 1H), 3.62 (m, 2H), 3.76 (m, 1H), 3.85 (m, 2H), 4.16 (m, 2H), 4.84 (tt, J=11.6, 4.2 Hz, 1H), 8.08 (s, 1H), 8.74 (s, 2H), 9.16 (s, 1H), 9.67 (br s, 1H) |
| 30      | Ex. 18   | P8          | 6-[(1R)-1-(3-pyridazin-3-ylazetidin-1-yl)ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one           | 382.2,<br>APCI     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) Partial spectrum: 1.35 (d, J=6.8 Hz, 3H), 1.92 (m, 2H), 2.38 (m, 2H), 3.85 (m, 1H), 4.02 (m, 1H), 4.85 (m, 1H), 7.47 (m, 2H), 8.07 (s, 1H), 9.14 (dd, J=3.3, 3.3 Hz, 1H)   |
| 31      | Ex. 1; heated 18h,<br>final purification<br>gradient 0-10%<br>EtOH/EtOAc | P10         | 1-cyclopentyl-6-[(1R)-1-[3-(2-methylpyrimidin-4-yl)azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                | 380.2,<br>LCMS     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.34 (d, J=6.8 Hz, 3H), 1.73 (m, 2H), 1.98 (m, 2H), 2.12 (m, 4H), 2.75 (s, 3H), 3.48 (m, 1H), 3.57 (q, J=6.7 Hz, 1H), 3.61 (m, 1H), 3.72-3.79 (m, 3H), 5.17 (m, 1H), 7.06 (d, J=5.2 Hz, 1H), 8.07 (s, 1H), 8.58 (d, J=5.2 Hz, 1H), 9.73 (br s, 1H)                                       |
| 32      | Ex. 31   | P10         | 6-[(1R)-1-[3-(2-methylpyrimidin-4-yl)azetidin-1-yl]ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 396.1,<br>LCMS     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.35 (d, J=6.8 Hz, 3H), 1.92 (m, 2H), 2.39 (m, 2H), 2.75 (s, 3H), 3.48 (m, 1H), 3.56-3.66 (m, 4H), 3.77 (m, 3H), 4.15 (m, 2H), 4.84 (tt, J=11.8, 4.2 Hz, 1H), 7.06 (d, J=5.2 Hz, 1H), 8.07 (s, 1H), 8.58 (d, J=5.2 Hz, 1H), 9.79 (br s, 1H)  |

| Ex. No. | Prep'n Method   | Side Chain*        | IUPAC Name  | MS<br>m/z<br>(M+1) | <sup>13</sup> C NMR (100 MHz), CDCl <sub>3</sub> (unless otherwise indicated),<br>observed peaks, δ (ppm); additional data   |
|---------|---|--------------------|---|--------------------|--|
| 33      | Ex. 31  | P3                 | 6-({(1R)-1-[3-(3-fluorobenzyl)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 414.1              | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.35 (d, J=6.6 Hz, 3H), 1.92 (m, 2H), 2.39 (m, 2H), 3.22 (m, 1H), 3.40 (m, 1H), 3.55 (q, J=6.7 Hz, 1H), 3.62 (m, 2H), 3.86 (m, 2H), 4.15 (m, 2H), 4.78-4.87 (m, 2H), 6.50 (m, 1H), 6.56 (m, 1H), 6.70 (m, 1H), 7.22 (m, 1H), 8.07 (s, 1H), 9.71 (br s, 1H)  |
| 34      | Ex. 31  | C37<br>(see Ex. 7) | 1-cyclopentyl-6-[(1R)-1-(3-quinolin-2-ylazetidin-1-yl)ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                    | 415.1,<br>LCMS     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.37 (d, J=6.8 Hz, 3H), 1.73 (m, 2H), 1.98 (m, 2H), 2.12 (m, 4H), 3.61 (m, 2H), 3.77 (m, 1H), 3.86 (m, 2H), 4.05 (m, 1H), 5.18 (m, 1H), 7.40 (d, J=8.5 Hz, 1H), 7.53 (ddd, J=8.1, 6.9, 1.1 Hz, 1H), 7.73 (ddd, J=8.5, 6.8, 1.5 Hz, 1H), 7.82 (br d, J=8.1 Hz, 1H), 8.07 (s, 1H), 8.08 (br d, J=8.5 Hz, 1H), 8.14 (d, J=8.5 Hz, 1H), 9.84 (br s, 1H) |
| 35      | Ex. 3;<br>NaH, 50°C, 5h, final<br>purification eluant<br>9:1 EtOAc/EtOH | P11                | 1-cyclopentyl-6-[(1R)-1-[(3R)-3-(pyrimidin-2-yloxy)pyrrolidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one       | 396.1,<br>LCMS     | (CD <sub>3</sub> OD) 18.24, 25.82, 32.94, 33.36, 33.48, 51.06, 58.51, 59.27, 63.76, 77.90, 106.03, 116.64, 135.38, 153.44, 160.83, 162.85, 165.85  |
| 36      | Ex. 1; 50°C, 24h,<br>final purification<br>eluant EtOAc                 | P11                | 1-cyclopentyl-6-[(1R)-1-[(3S)-3-(pyrimidin-2-yloxy)pyrrolidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one       | 396.1,<br>LCMS     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.46 (d, J=6.6 Hz, 3H), 1.70 (m, 2H), 1.96 (m, 2H), 2.09 (m, 5H), 2.32 (m, 1H), 2.76-2.89 (m, 3H), 3.23 (m, 1H), 3.55 (m, 1H), 5.14 (m, 1H), 5.44 (m, 1H), 6.93 (m, 1H), 8.05 (s, 1H), 8.49 (d, J=4.6 Hz, 2H), 9.90 (br s, 1H)  |

| Ex. No. | Prep'n Method   | Side Chain*        | IUPAC Name   | MS<br><i>m/z</i><br>( <i>M</i> +1) | <sup>13</sup> C NMR (100 MHz), CDCl <sub>3</sub> (unless otherwise indicated),<br>observed peaks, $\delta$ (ppm); additional data  |
|---------|---|--------------------|--|------------------------------------|--|
| 37      | Ex. 1;<br>2-chloro-2-oxo-1-phenylethyl acetate used; K <sub>2</sub> CO <sub>3</sub> /CH <sub>3</sub> CN final step; purification eluant 2% MeOH/CH <sub>2</sub> Cl <sub>2</sub> | com'l              | 6-[(3-phenoxazetidin-1-yl)(phenyl)methyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                         | 458.3,<br>LCMS                     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.90 (m, 2H), 2.36 (m, 2H), 3.26 (dd, <i>J</i> =8.3, 5.4 Hz, 1H), 3.34 (dd, <i>J</i> =7.9, 5.6 Hz, 1H), 3.62 (m, 2H), 3.76 (br dd, <i>J</i> =7.2, 7.2 Hz, 1H), 3.93 (br dd, <i>J</i> =7.1, 7.1 Hz, 1H), 4.15 (m, 2H), 4.58 (s, 1H), 4.85 (m, 2H), 6.76 (br d, <i>J</i> =8.6 Hz, 2H), 6.97 (t, <i>J</i> =7.4 Hz, 1H), 7.27 (m, 2H), 7.36 (m, 3H), 7.48 (br d, <i>J</i> =7.9 Hz, 2H), 8.05 (s, 1H), 9.98 (br s, 1H)   |
| 38      | Ex. 1;<br>K <sub>2</sub> CO <sub>3</sub> /CH <sub>3</sub> CN final step; purification gradient 1-2.5% MeOH/CH <sub>2</sub> Cl <sub>2</sub>                                      | Com'l              | 6-[(1 <i>R</i> )-1-(3-phenoxazetidin-1-yl)ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                  | 396.4,<br>LCMS                     | <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) 1.38 (d, <i>J</i> =6.8 Hz, 3H), 1.89 (m, 2H), 2.29 (m, 2H), 3.28 (dd, assumed, partially obscured by solvent peak, <i>J</i> =8.1, 5.2 Hz, 1H), 3.34 (dd, assumed, partially obscured by solvent peak, <i>J</i> =7.9, 5.4 Hz, 1H), 3.61 (m, 3H), 3.85 (dd, <i>J</i> =7.0, 7.0 Hz, 1H), 3.93 (dd, <i>J</i> =6.9, 6.9 Hz, 1H), 4.08 (m, 2H), 4.87 (m, 1H), 4.98 (tt, <i>J</i> =11.7, 4.2 Hz, 1H), 6.80 (d, <i>J</i> =8.2 Hz, 2H), 6.93 (t, <i>J</i> =7.8 Hz, 1H), 7.26 (dd, <i>J</i> =7.8, 7.8 Hz, 2H), 8.03 (s, 1H) |
| 39      | Ex. 1;<br>(1 <i>S</i> )-1-(chlorocarbonyl) propyl acetate used  | C39<br>(see Ex. 8) | 6-[(1 <i>R</i> )-1-[3-(6-methylpyridin-2-yl)azetidin-1-yl]propyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 409.1,<br>LCMS                     | 9.18, 24.51, 25.12, 32.03, 32.20, 36.88, 53.84, 57.74, 58.73, 66.98, 70.96, 105.34, 118.33, 121.22, 134.63, 136.61, 151.68, 157.75, 158.04, 159.13, 159.73   |

| Ex. No. | Prep'n Method | Side Chain*         | IUPAC Name  | MS<br>m/z<br>(M+1) | <sup>13</sup> C NMR (100 MHz), CDCl <sub>3</sub> (unless otherwise indicated),<br>observed peaks, δ (ppm); additional data                           |
|---------|---------------|---------------------|---|--------------------|--|
| 40      | Ex. 39        | P4                  | 6-[(1R)-1-(3-pyridin-2-ylazetidin-1-yl)propyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one             | 395.1,<br>LCMS     | 9.23, 25.17, 32.09, 32.20, 36.94, 53.91, 57.53, 58.89, 67.03, 70.94, 105.38, 121.83, 121.95, 134.65, 136.47, 149.45, 157.77, 159.11, 160.22          |
| 41      | Ex. 39        | P12                 | 6-[(1R)-1-[3-(5-methylpyrimidin-2-yl)azetidin-1-yl]propyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 410.2,<br>LCMS     | 9.29, 15.39, 32.08, 32.21, 53.97, 57.08, 57.92, 67.03, 134.69, 157.29 (only peaks observed)  |
| 42      | Ex. 39        | C42<br>(see Ex. 10) | 6-[(1R)-1-[3-(5-chloropyrimidin-2-yl)azetidin-1-yl]propyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 430.1,<br>LCMS     | 9.24, 25.06, 32.06, 32.21, 37.25, 53.96, 57.04, 57.95, 67.03, 70.88, 134.68, 155.60 (only peaks observed)  |
| 43      | Ex. 1         | P18                 | 1-cyclopentyl-6-[(1R)-1-[3-[(6-methylpyridin-3-yl)methyl]azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one           | 393.2,<br>LCMS     | 18.06, 23.86, 24.66, 31.13, 32.37, 36.57, 57.56, 57.65, 58.16, 65.38, 105.00, 122.94, 131.66, 134.46, 136.07, 148.84, 151.99, 156.33, 157.86, 160.23 |

| Ex. No. | Prep'n Method  | Side Chain* | IUPAC Name  | MS<br><i>m/z</i><br>(M+1) | <sup>13</sup> C NMR (100 MHz), CDCl <sub>3</sub> (unless otherwise indicated),<br>observed peaks, $\delta$ (ppm); additional data  |
|---------|--|-------------|---|---------------------------|--|
| 44      | Ex. 1  | P13         | 6-((1R)-1-[3-(pyrimidin-2-ylmethyl)azetidin-1-yl]ethyl)-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                  | 396.1,<br>LCMS            | 18.20, 29.32, 32.16, 43.17, 53.74, 57.89, 58.68, 65.40, 67.01, 105.32, 118.80, 134.71, 157.03, 160.83  |
| 45      | Ex. 1;<br>final purification<br>eluant 10%<br>MeOH/EtOAc                               | P14         | 1:1 <i>cis</i> - and <i>trans</i> -1-cyclopentyl-6-[[1-(1R)-1-(3-pyrimidin-2-ylpyrrolidin-1-yl)ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 380.2,<br>LCMS            | 13.32, 14.02, 20.23, 20.96, 22.59, 24.67, 24.72, 30.59, 30.80, 32.28, 32.31, 32.36, 45.04, 45.30, 49.45, 50.81, 51.83, 56.59, 57.50, 57.60, 58.20, 61.18, 104.92, 105.13, 118.78, 134.28, 134.35, 152.34, 152.45, 157.50, 158.58, 158.67, 161.65, 162.47 |
| 46      | Ex. 1;<br>final purification<br>eluant 94:5:1<br>EtOAc/MeOH/<br>NH <sub>4</sub> OH     | P12         | 1-cyclopentyl-6-((1R)-1-[3-(5-methylpyrimidin-2-yl)azetidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                               | 380.1,<br>APCI            | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.33 (d, <i>J</i> =6.6 Hz, 3H), 1.70 (m, 2H), 1.95 (m, 2H), 2.09 (m, 4H), 2.30 (s, 3H), 3.58 (br m, 2H), 3.69 (br m, 1H), 3.79 (br m, 2H), 3.97 (m, 1H), 5.15 (m, 1H), 8.04 (s, 1H), 8.53 (s, 2H)       |
| 47      | Ex. 1;<br>final purification<br>gradient 0-20%<br>MeOH/CH <sub>2</sub> Cl <sub>2</sub> | P12         | 6-((1R)-1-[3-(5-methylpyrimidin-2-yl)azetidin-1-yl]ethyl)-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                | 396.1,<br>APCI            | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.35 (d, <i>J</i> =6.4 Hz, 3H), 1.91 (m, 2H), 2.32 (s, 3H), 2.37 (m, 2H), 3.56-4.01 (m, 6H), 3.61 (m, 2H), 4.14 (m, 2H), 4.85 (m, 1H), 8.05 (s, 1H), 8.55 (s, 2H)                                       |

| Ex. No. | Prep'n Method  | Side Chain* | IUPAC Name  | MS<br>m/z<br>(M+1) | <sup>13</sup> C NMR (100 MHz), CDCl <sub>3</sub> (unless otherwise indicated),<br>observed peaks, δ (ppm); additional data  |
|---------|--|-------------|---|--------------------|---|
| 48      | Ex. 1;<br>final purification<br>preparative TLC;<br>eluant 92:7:1<br>EtOAc/MeOH/<br>NH <sub>4</sub> OH | P16         | 6-((1R)-1-[3-(5-cyclopropylpyrimidin-2-yl)azetidin-1-yl]ethyl)-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 422.1,<br>APCI     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 0.76 (m, 2H), 1.07 (m, 2H), 1.32 (d, J=6.8 Hz, 3H), 1.84 (m, 1H), 1.89 (m, 2H), 2.34 (m, 2H), 3.52-3.67 (m, 5H), 3.76 (dd, J=3.7, 3.7 Hz, 2H), 3.94 (m, 1H), 4.11 (br d, J=11.3 Hz, 2H), 4.83 (m, 1H), 8.03 (s, 1H), 8.42 (s, 2H)                            |
| 49      | Ex. 48   | P16         | 1-cyclopentyl-6-((1R)-1-[3-(5-cyclopropylpyrimidin-2-yl)azetidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                | 406.1,<br>APCI     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 0.78 (m, 2H), 1.09 (m, 2H), 1.32 (d, J=6.8 Hz, 3H), 1.71 (m, 2H), 1.86 (tt, J=8.5, 5.1 Hz, 1H), 1.96 (m, 2H), 2.10 (m, 4H), 3.56 (m, 2H), 3.67 (dd, J=7.0, 7.0 Hz, 1H), 3.76 (dd, J=7.5, 7.5 Hz, 2H), 3.95 (m, 1H), 5.16 (m, 1H), 8.05 (s, 1H), 8.44 (s, 2H) |
| 50      | Ex. 1;<br>final purification<br>gradient 0-100%<br>(10% MeOH/<br>EtOAc)/heptane                        | P15         | 6-((1R)-1-[3-(4,6-dimethylpyrimidin-2-yl)azetidin-1-yl]ethyl)-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one  | 410.1,<br>APCI     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.32 (d, J=6.6 Hz, 3H), 1.91 (br d, J=12.5 Hz, 2H), 2.37 (m, 2H), 2.46 (s, 6H), 3.54-3.64 (m, 4H), 3.69 (dd, J=7.0, 7.0 Hz, 1H), 3.75 (m, 2H), 3.89 (m, 1H), 4.13 (m, 2H), 4.83 (tt, J=11.7, 4.2 Hz, 1H), 6.89 (s, 1H), 8.05 (s, 1H)                         |
| 51      | Ex. 47   | P15         | 1-cyclopentyl-6-((1R)-1-[3-(4,6-dimethylpyrimidin-2-yl)azetidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                 | 394.1,<br>APCI     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.32 (d, J=6.8 Hz, 3H), 1.72 (m, 2H), 1.97 (m, 2H), 2.10 (m, 4H), 2.47 (s, 6H), 3.58 (m, 2H), 3.70 (dd, J=7.0, 7.0 Hz, 1H), 3.75 (m, 2H), 3.89 (m, 1H), 5.16 (m, 1H), 6.89 (s, 1H), 8.05 (s, 1H)   |

| Ex. No. | Prep'n Method  | Side Chain* | IUPAC Name   | MS<br>m/z<br>(M+1) | <sup>13</sup> C NMR (100 MHz), CDCl <sub>3</sub> (unless otherwise indicated),<br>observed peaks, δ (ppm); additional data   |
|---------|--|-------------|--|--------------------|--|
| 52      | Ex. 47   | P17         | 1-cyclopentyl-6-((1R)-1-[3-(4-methylpyrimidin-2-yl)azetidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                | 380.1,<br>APCI     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.32 (d, J=6.6 Hz, 3H), 1.70 (m, 2H), 1.96 (m, 2H), 2.09 (m, 4H), 2.52 (s, 3H), 3.57 (m, 2H), 3.69 (dd, J=7.0, 7.0 Hz, 1H), 3.76 (m, 2H), 3.94 (m, 1H), 5.16 (m, 1H), 7.03 (d, J=5.2 Hz, 1H), 8.05 (s, 1H), 8.55 (d, J=5.2 Hz, 1H), 9.89 (br s, 1H)   |
| 53      | Ex. 47   | P17         | 6-((1R)-1-[3-(4-methylpyrimidin-2-yl)azetidin-1-yl]ethyl)-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 396.1,<br>APCI     | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.33 (d, J=6.6 Hz, 3H), 1.91 (m, 2H), 2.38 (m, 2H), 2.53 (s, 3H), 3.57-3.65 (m, 4H), 3.71 (dd, J=6.9, 6.9 Hz, 1H), 3.78 (m, 2H), 3.95 (m, 1H), 4.14 (m, 2H), 4.84 (m, 1H), 7.05 (d, J=5.2 Hz, 1H), 8.06 (s, 1H), 8.56 (d, J=5.2 Hz, 1H)   |
| 54      | Ex. 4;<br>NEt <sub>3</sub> added to<br>reaction; purified by<br>HPLC, gradient 30-<br>70% CH <sub>3</sub> CN/water<br>with constant 0.1%<br>NH <sub>4</sub> OH | P19         | 4-[(1-{1-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]ethyl}azetidin-3-yl)oxy]benzonitrile       | 421.5,<br>LCMS     | <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) 1.38 (d, J=6.6 Hz, 3H), 1.89 (m, 2H), 2.29 (m, 2H), 3.30 (m, 1H, assumed, obscured by solvent peak), 3.37 (dd, J=8.1, 5.2 Hz, 1H), 3.61 (m, 3H), 3.88 (dd, J=7.0, 7.0 Hz, 1H), 3.94 (dd, J=7.1, 7.1 Hz, 1H), 4.09 (m, 2H), 4.97 (m, 2H), 6.98 (d, J=8.7 Hz, 2H), 7.65 (d, J=8.7 Hz, 2H), 8.03 (s, 1H) |
| 55      | Ex. 4;<br>final purification<br>eluant 100:1<br>CHCl <sub>3</sub> /MeOH  | P19         | 4-[(1-{1-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)ethyl}azetidin-3-yl)oxy]benzonitrile                      | 405.0,<br>APCI     | 17.96, 24.71, 32.39, 32.44, 57.78, 58.41, 59.86, 65.14, 66.07, 105.05, 115.31, 118.78, 134.17, 134.56, 159.92  |

| Ex. No. | Prep'n Method  | Side Chain* | IUPAC Name   | MS<br>m/z<br>(M+1) | <sup>13</sup> C NMR (100 MHz), CDCl <sub>3</sub> (unless otherwise indicated),<br>observed peaks, δ (ppm); additional data                                       |
|---------|--|-------------|--|--------------------|--|
| 56      | Ex. 4;<br>final purification<br>Chiralpak AD; eluant<br>75:25 heptane/IPA                                | P20         | 1-cyclopentyl-6-[(1S)-1-[3-(4-methylphenoxy)azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one           | 394.0,<br>APCI     | 18.05, 20.43, 24.72, 32.39, 32.44, 57.77, 58.79, 60.55, 65.20, 65.62, 105.07, 114.40, 130.09, 130.80, 134.56, 151.96, 154.55, 157.90; First enantiomer to elute  |
| 57      | Ex. 56   | P20         | 1-cyclopentyl-6-[(1R)-1-[3-(4-methylphenoxy)azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one           | 394.1,<br>APCI     | 18.05, 20.43, 24.72, 32.41, 32.45, 57.78, 58.79, 60.55, 65.20, 65.63, 105.08, 114.42, 130.09, 130.82, 134.57, 151.98, 154.55, 157.90; Second enantiomer to elute |
| 58      | Ex. 4  | P20         | 6-{1-[3-(4-methylphenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 410.0,<br>APCI     | 18.13, 20.43, 32.18, 53.79, 58.80, 60.58, 65.20, 65.62, 67.00, 105.29, 114.39, 130.09, 130.82, 134.74, 151.77, 154.54, 157.75, 160.17                            |
| 59      | Ex. 4;<br>final purification<br>Chiralcel OD, 10 x<br>50 cm, 250 mL/min;<br>eluant 65:35<br>heptane/EtOH | com'l       | 1-cyclopentyl-6-[(1S)-1-(3-phenoxyazetidin-1-yl)ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                     | 380.0,<br>APCI     | 18.07, 24.72, 32.39, 32.44, 57.77, 58.77, 60.49, 65.22, 65.53, 105.08, 114.55, 121.47, 129.67, 134.57, 151.96, 156.69, 157.93; Retention time 18 mins            |



| Ex. No. | Prep'n Method                             | Side Chain* | IUPAC Name   | MS<br><i>m/z</i><br>( <i>M</i> +1) | <sup>13</sup> C NMR (100 MHz), CDCl <sub>3</sub> (unless otherwise indicated),<br>observed peaks, $\delta$ (ppm); additional data                        |
|---------|---|-------------|--|------------------------------------|--|
| 60      | Ex. 59                                    | com'l       | 1-cyclopentyl-6-[(1 <i>R</i> )-1-(3-phenoxypyrazetidin-1-yl)ethyl]-1,5-dihydro-4 <i>H</i> -pyrazolo[3,4- <i>d</i> ]pyrimidin-4-one                   | 380.0,<br>APCI                     | 18.07, 24.72, 32.39, 32.45, 57.77, 58.77, 60.49, 65.23, 65.55, 105.08, 114.55, 121.47, 129.67, 134.57, 151.98, 156.69, 157.93;<br>Retention time 26 mins |
| 61      | Ex. 4;<br>2-bromobutanoyl<br>bromide used | comm'l      | 6-[1-(3-phenoxypyrazetidin-1-yl)propyl]-1-(tetrahydro-2 <i>H</i> -pyran-4-yl)-1,5-dihydro-4 <i>H</i> -pyrazolo[3,4- <i>d</i> ]pyrimidin-4-one        | 410.0,<br>APCI                     | 9.18, 25.29, 32.06, 32.18, 53.96, 59.07, 60.61, 65.69, 67.00, 71.15, 105.35, 114.53, 121.47, 129.65, 134.68, 151.56, 156.65, 157.69                      |
| 62      | Ex. 61                                    | P20         | 6-[1-[3-(4-methylphenoxy)azetidin-1-yl]propyl]-1-(tetrahydro-2 <i>H</i> -pyran-4-yl)-1,5-dihydro-4 <i>H</i> -pyrazolo[3,4- <i>d</i> ]pyrimidin-4-one | 424.0,<br>APCI                     | 9.18, 20.43, 25.29, 32.08, 32.20, 53.96, 59.10, 60.69, 65.80, 67.00, 71.14, 105.37, 114.40, 130.09, 130.83, 134.69, 151.58, 157.72                       |
| 63      | Ex. 4                                     | P20         | 1-isopropyl-6-{1-[3-(4-methylphenoxy)azetidin-1-yl]ethyl}-1,5-dihydro-4 <i>H</i> -pyrazolo[3,4- <i>d</i> ]pyrimidin-4-one                            | 368.0,<br>APCI                     | 18.04, 20.43, 22.03, 49.16, 58.77, 60.57, 65.17, 65.63, 105.08, 114.42, 130.09, 130.80, 134.54, 140.88, 151.43, 154.57, 157.92                           |
| 64      | Ex. 61                                    | P21         | 6-[1-[3-(pyridin-2-yloxy)azetidin-1-yl]propyl]-1-(tetrahydro-2 <i>H</i> -pyran-4-yl)-1,5-dihydro-4 <i>H</i> -pyrazolo[3,4- <i>d</i> ]pyrimidin-4-one | 411.0,<br>APCI                     | 9.14, 25.36, 32.03, 32.15, 53.87, 59.31, 60.49, 64.54, 66.97, 71.18, 105.34, 110.90, 117.24, 134.65, 138.76, 146.90, 151.62, 157.71, 158.87, 162.36      |

| Ex. No. | Prep'n Method | Side Chain* | IUPAC Name  | MS<br><i>m/z</i><br>( <i>M</i> +1) | <sup>13</sup> C NMR (100 MHz), CDCl <sub>3</sub> (unless otherwise indicated),<br>observed peaks, $\delta$ (ppm); additional data    |
|---------|---------------|-------------|---|------------------------------------|--|
| 65      | Ex. 61        | com'l       | 1-isopropyl-6-[1-(3-phenoxyazetidin-1-yl)propyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                              | 368.0,<br>APCI                     | 9.18, 21.92, 22.04, 25.30, 49.29, 59.04, 60.60, 65.75, 71.26, 105.14, 114.55, 121.43, 129.64, 134.47, 151.25, 156.71, 157.81, 158.28 |
| 66      | Ex. 61        | P20         | 1-isopropyl-6-{1-[3-(4-methylphenoxy)azetidin-1-yl]propyl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                    | 382.0,<br>APCI                     | 9.17, 20.41, 21.91, 22.03, 25.32, 49.28, 59.04, 60.67, 65.84, 71.26, 105.14, 114.40, 130.06, 130.75, 134.45, 154.58, 157.80, 158.37  |
| 67      | Ex. 4         | P22         | 6-{1-[3-(pyrazin-2-yloxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one    | 398.0,<br>APCI                     | 18.11, 32.15, 53.82, 58.73, 60.10, 64.92, 65.23, 67.00, 105.31, 134.75, 135.74, 137.31, 140.55, 157.83, 158.86                       |
| 68      | Ex. 3         | com'l       | 6-{1-[3-(quinoxalin-2-yloxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 448.0,<br>APCI                     | 18.13, 32.15, 53.81, 58.73, 60.28, 65.11, 65.26, 66.98, 105.31, 127.01, 127.31, 128.98, 130.34, 134.75, 138.94, 155.81               |
| 69      | Ex. 4         | P23         | 6-{1-[3-(pyrimidin-2-yloxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one  | 398.0,<br>APCI                     | 18.14, 32.17, 53.73, 58.49, 60.30, 65.20, 65.32, 67.00, 105.28, 115.63, 134.74, 151.76, 157.75, 159.41                               |

| Ex. No. | Prep'n Method | Side Chain* | IUPAC Name   | MS<br>m/z<br>(M+1) | <sup>13</sup> C NMR (100 MHz), CDCl <sub>3</sub> (unless otherwise indicated),<br>observed peaks, δ (ppm); additional data   |
|---------|---------------|-------------|--|--------------------|--|
| 70      | Ex. 3         | com'l       | 6-{1-[3-(quinolin-2-yloxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one            | 447.0,<br>APCI     | 18.23 (br), 32.15, 53.76, 59.04, 60.64, 64.51, 65.26 (br), 67.00, 112.50, 124.34, 125.15, 127.40, 129.64, 134.74, 139.10, 146.28, 157.86, 160.46                           |
| 71      | Ex. 3         | com'l       | 6-{1-[3-(phthalazin-1-yloxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one          | 448.0,<br>APCI     | 18.20, 32.14, 53.73, 59.26, 59.85, 65.29, 66.29, 66.97, 105.28, 119.47, 122.74, 125.90, 128.86, 132.30, 132.52, 134.71, 148.35, 151.73, 157.78, 160.16                     |
| 72      | Ex. 3         | com'l       | 6-{1-[3-[(6-methylpyridazin-3-yl)oxy]azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 412.0,<br>APCI     | 18.17, 21.39, 32.13, 53.66, 59.13, 59.70, 65.13, 65.88, 66.97, 105.24, 117.29, 130.26, 134.70, 151.70, 155.77, 157.81, 162.34<br>dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one |
| 73      | Ex. 3         | com'l       | 6-{1-[3-(pyrimidin-4-yloxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one           | 398.4,<br>LCMS     | 18.05 (br), 32.17, 53.87, 58.73, 59.83, 65.13, 67.00, 105.32, 108.61, 134.75, 157.54, 158.37   |

| Ex. No. | Prep'n Method   | Side Chain* | IUPAC Name   | MS <i>m/z</i> (M+1) | <sup>13</sup> C NMR (100 MHz), CDCl <sub>3</sub> (unless otherwise indicated), observed peaks, δ (ppm); additional data  |
|---------|---|-------------|--|---------------------|--|
| 74      | Ex. 3   | com'l       | 6-{1-[3-[(4,6-dimethylpyrimidin-2-yl)oxy]azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 426.4, LCMS         | 18.13 (br), 23.78, 32.15, 53.70, 58.46, 60.58, 64.75, 65.11 (br), 66.98, 105.28, 114.46, 134.72, 169.46  |
| 75      | Ex. 3   | P29         | 6-{1-[3-(pyrido[2,3-d]pyrimidin-2-yl)oxy]azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 449.0, APCI         | 18.20, 32.14, 53.70, 58.76, 59.89, 65.40, 66.35, 66.98, 105.29, 116.30, 121.41, 134.75, 136.74, 158.31, 165.33   |
| 76      | Ex. 3   | com'l       | 6-{1-[3-(quinazolin-2-yl)oxy]azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one             | 448.3, LCMS         | 18.16 (br), 32.17, 53.72, 58.53, 60.57, 65.23, 65.37, 67.00, 122.01, 125.47, 126.78, 127.37, 134.74, 163.88  |
| 77      | Ex. 4; final purification Chiralcel OD-H, 4.6 mm x 25 cm, 1 mL/min, eluant 85:15 heptane/EtOH | P21         | 6-[(1R)-1-[3-(pyridin-2-yl)oxy]azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one           | 397.0, APCI         | 18.23, 32.14, 53.75, 59.07, 60.40, 64.33, 65.25, 67.00, 105.31, 110.92, 117.29, 134.72, 138.78, 146.93, 157.74, 162.34; retention time 13.32 min, second enantiomer to elute |

| Ex. No. | Prep'n Method   | Side Chain* | IUPAC Name  | MS<br>m/z<br>(M+1) | <sup>13</sup> C NMR (100 MHz), CDCl <sub>3</sub> (unless otherwise indicated),<br>observed peaks, δ (ppm); additional data   |
|---------|---|-------------|---|--------------------|--|
| 78      | Ex. 3   | com'l       | 6-{1-[3-(1,8-naphthyridin-2-yloxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one     | 448.0,<br>APCI     | 18.22, 32.14, 32.18, 53.75, 59.29, 59.77, 65.29, 65.47, 67.00, 105.32, 114.18, 119.50, 120.26, 134.75, 136.71, 139.58, 151.73, 152.89, 154.99, 157.71, 163.27  |
| 79      | Ex. 3   | com'l       | 6-(1-[3-[(3-methylquinoxalin-2-yl)oxy]azetidin-1-yl]ethyl)-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one | 462.0,<br>APCI     | 18.23 (br), 20.26, 32.14, 53.82, 58.85, 60.48, 65.13, 65.34 (br), 67.00, 105.32, 126.84, 126.90, 128.02, 129.04, 134.75, 138.78, 139.46, 147.46, 154.82, 157.81  |
| 80      | Ex. 4   | P24         | 1-cyclopentyl-6-(1-[3-[(4,6-dimethylpyrimidin-2-yl)oxy]azetidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one             | 410.0,<br>APCI     | 18.10, 23.78, 24.69, 32.38, 57.71, 58.41, 60.60, 64.81, 65.20, 105.04, 114.42, 134.53, 157.90, 163.67, 169.43  |
| 81      | Ex. 1; CH <sub>3</sub> CN, K <sub>2</sub> CO <sub>3</sub> ; purification eluant 5% MeOH/CHCl <sub>3</sub> | P25         | 6-[(1R)-1-(3-benzyl-3-hydroxyazetidin-1-yl)ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one          | 410.1,<br>LCMS     | <sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ) 1.31 (d, J=6.7 Hz, 3H), 1.90 (m, 2H), 2.38 (m, 2H), 3.05 (s, 2H), 3.21-3.54 (m, 5H), 3.61 (m, 2H), 4.14 (m, 2H), 4.83 (m, 1H), 7.30 (m, 5H), 8.15 (s, 1H) |

| Ex. No. | Prep'n Method  | Side Chain* | IUPAC Name  | MS<br><i>m/z</i><br>(M+1) | <sup>13</sup> C NMR (100 MHz, CDCl <sub>3</sub> ) (unless otherwise indicated),<br>observed peaks, $\delta$ (ppm); additional data   |
|---------|--|-------------|---|---------------------------|--|
| 82      | Ex. 81   | P26         | 6-[(1R)-1-(3-benzyl-3-fluoroazetidin-1-yl)ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one             | 412.2,<br>LCMS            | <sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ) 1.32 (d, J=6.7 Hz, 3H), 1.91 (m, 2H), 2.37 (m, 2H), 2.76-3.66 (m, 8H), 3.86 (m, 1H), 4.14 (m, 2H), 4.83 (m, 1H), 7.12-7.36 (m, 5H), 8.05 (s, 1H)  |
| 83      | Ex. 1; CH <sub>3</sub> CN;<br>purification eluant<br>5% MeOH/CHCl <sub>3</sub> | P27         | 6-[(1R)-1-(3-benzylazetidin-1-yl)ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                      | 394.2,<br>LCMS            | <sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ) 1.27 (d, J=6.7 Hz, 3H), 1.91 (m, 2H), 2.37 (m, 2H), 2.79 (m, 1H), 2.91 (m, 3H), 3.05 (dd, J=6.6, 6.6 Hz, 1H), 3.42 (m, 3H), 3.61 (m, 2H), 4.14 (m, 2H), 4.83 (m, 1H), 7.12-7.31 (m, 5H), 8.05 (s, 1H)   |
| 84      | Ex. 5  | com'l       | 2-chloro-4-[(1-{1-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]ethyl}azetidin-3-yl)oxy]benzonitrile | 455.3,<br>LCMS            | <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) 1.38 (d, J=6.6 Hz, 3H), 1.89 (m, 2H), 2.29 (m, 2H), 3.31 (m, 1H, assumed, obscured by solvent peak), 3.38 (dd, J=8.1, 5.2 Hz, 1H), 3.61 (m, 3H), 3.87 (dd, J=7.1, 7.1 Hz, 1H), 3.93 (dd, J=7.1, 7.1 Hz, 1H), 4.09 (m, 2H), 4.98 (m, 2H), 6.95 (dd, J=8.7, 2.5 Hz, 1H), 7.11 (d, J=2.5 Hz, 1H), 7.71 (d, J=8.7 Hz, 1H), 8.03 (s, 1H) |
| 85      | Ex. 5; microwave<br>reaction, 1h, 140°C,<br>75W                                | com'l       | 2-fluoro-4-[(1-{1-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]ethyl}azetidin-3-yl)oxy]benzonitrile | 439.4,<br>LCMS            | <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) 1.37 (d, J=6.6 Hz, 3H), 1.89 (m, 2H), 2.29 (m, 2H), 3.31 (m, 1H, assumed, obscured by solvent peak), 3.38 (dd, J=8.3, 5.0 Hz, 1H), 3.62 (m, 3H), 3.87 (dd, J=7.1, 7.1 Hz, 1H), 3.94 (dd, J=7.0, 7.0 Hz, 1H), 4.09 (br d, J=11.6 Hz, 2H), 4.97 (m, 2H), 6.85 (m, 2H), 7.66 (dd, J=8.1, 8.1 Hz, 1H), 8.03 (s, 1H)                     |

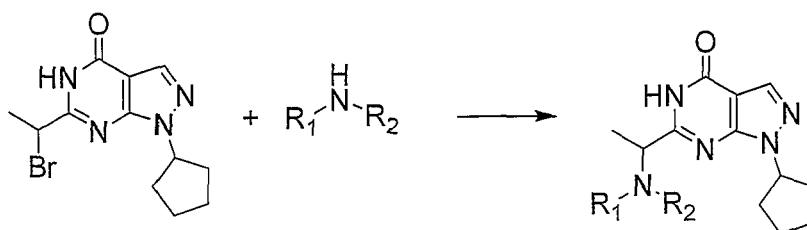
| Ex. No. | Prep'n Method | Side Chain* | IUPAC Name   | MS<br><i>m/z</i><br>(M+1) | <sup>13</sup> C NMR (100 MHz), CDCl <sub>3</sub> (unless otherwise indicated),<br>observed peaks, $\delta$ (ppm); additional data   |
|---------|---------------|-------------|--|---------------------------|---|
| 86      | Ex. 5         | com'l       | 3-[(1-{1-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]ethyl}azetidin-3-yl)oxy]benzonitrile | 421.4,<br>LCMS            | <sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) 1.37 (d, J=6.6 Hz, 3H), 1.89 (m, 2H), 2.29 (m, 2H), 3.29 (m, 1H, assumed, obscured by solvent peak), 3.35 (dd, J=8.2, 5.2 Hz, 1H), 3.61 (m, 3H), 3.87 (dd, J=7.0, 7.0 Hz, 1H), 3.93 (dd, J=7.0, 7.0 Hz, 1H), 4.08 (br d, J=11.6 Hz, 2H), 4.95 (m, 2H), 7.16 (m, 2H), 7.31 (br d, J=7.7 Hz, 1H), 7.45 (dd, J=7.9, 7.9 Hz, 1H), 8.02 (s, 1H)                               |
| 87      | Ex. 18        | P3          | 1-cyclopentyl-6-[(1R)-1-[3-(3-fluorobenzyl)azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                  | 398.1,<br>LCMS            | <sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) 1.34 (d, J=6.6 Hz, 3H), 1.72 (m, 2H), 1.97 (m, 2H), 2.10 (m, 4H), 3.22 (dd, J=7.6, 5.9 Hz, 1H), 3.37 (dd, J=7.4, 5.9 Hz, 1H), 3.54 (q, J=6.7 Hz, 1H), 3.85 (m, 2H), 4.80 (m, 1H), 5.16 (m, 1H), 6.48 (ddd, J=10.6, 2.3, 2.3 Hz, 1H), 6.55 (dd, J=8.3, 2.1 Hz, 1H), 6.68 (ddd, J=8.3, 8.3, 1.9 Hz, 1H), 7.21 (ddd, J=8.3, 8.3, 6.8 Hz, 1H), 8.05 (s, 1H), 9.85 (br s, 1H) |

• com'l = commercially available side chain

The compounds of additional Examples 88-175 were prepared in accordance with the following Methods A through E, as indicated in Table 3 below.

Method A

5 Preparation of N-substituted 6-(1-aminoethyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-ones

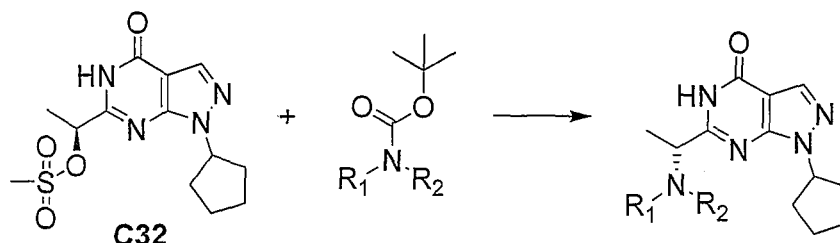


The amines (0.14 mmol) were weighed into vials and treated with a solution of 6-(1-bromoethyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (22 mg, 0.07 mmol, prepared in a manner analogous to the synthesis of **C25** in Example 5, except that **C29** was used in place of **C2**) in a 1:5 mixture of DMF: acetonitrile (0.6 mL). Potassium carbonate (29 mg, 0.21 mmol) was added, and the reactions were shaken and heated at 82°C for 8 h. The reactions were then cooled to room temperature and water (1.5 mL) and EtOAc (2.5 mL) were added. After vortexing the reactions, the organic portions were separated and passed through a short column of sodium sulfate. This process was repeated two times. The combined filtrates for each reaction were concentrated *in vacuo*, then treated with a 3% solution of trifluoroacetic acid in dichloromethane (0.5 mL). The mixtures were shaken for 15 mins, solvent removed *in vacuo*, and the crude samples were dissolved in DMSO (1 mL) and purified by preparative HPLC (column: Xterra PrepMS C<sub>18</sub>, 5 μm, 19 x 100 mm; Solvent A: 0.1% trifluoroacetic acid in water (v/v); Solvent B: acetonitrile; Gradient: 5% to 95% B), to afford the final Examples.



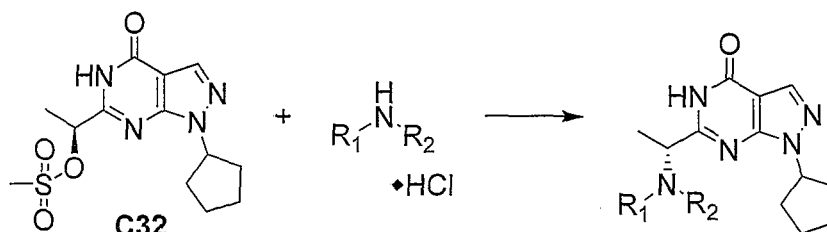
### Method B

#### Preparation of *N*-substituted 6-[(1*R*)-1-aminoethyl]-1-cyclopentyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-ones



- 5        The *t*-butoxycarbonyl-protected amines (0.1 mmol) were added to a solution of 1:1 trifluoroacetic acid: dichloromethane (0.75 mL) and shaken at room temperature for 18 h. The reactions were concentrated *in vacuo* and a 2.33 mM solution of triethylamine in 1:1 toluene: acetonitrile (0.15 mL) was added.        Next, (1*S*)-1-(1-cyclopentyl-4-oxo-4,5-dihydro-1*H*-pyrazolo[3,4-
- 10    *d*]pyrimidin-6-yl)ethyl methanesulfonate (**C32**, 16.3 mg, 0.05 mmol) dissolved in 1:1 toluene: acetonitrile (0.6 mL) was added, and the reactions were heated to 90°C for 8 h. The reactions were cooled to room temperature and left for 48 h, then 1N aqueous sodium hydroxide solution (1.5 mL) and EtOAc (2.2 mL) were added. The reactions were vortexed, and the organic layers were
- 15    separated and loaded onto a strong cation-exchange solid phase extraction (SCX SPE) cartridge. The extraction process was repeated two times, followed by a final wash of the SPE column with EtOAc (5 mL). The crude products were released by eluting the columns with a solution of triethylamine in MeOH (1N, 6 mL). The eluants were concentrated *in vacuo*, dissolved in
- 20    DMSO (1 mL) and purified by preparative HPLC (column: XBridge C<sub>18</sub>, 5 μm; 19 x 100 mm; Solvent A: 0.03% ammonium hydroxide in water (v/v); Solvent B: 0.03% ammonium hydroxide in acetonitrile (v/v); Gradient: 15% to 95% B), to provide the final Examples.

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Method CPreparation of N-substituted 6-[(1R)-1-aminoethyl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-ones

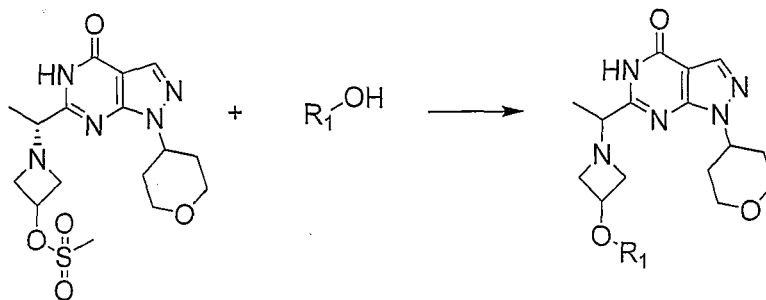
- 5        The amine hydrochloride salts (0.150 mmol) were dissolved in 1:1 dichloroethane: methanol (2.4 mL) and loaded onto SCX SPE columns. The source vials were rinsed with additional 1:1 dichloroethane: MeOH (2.4 mL), which was added to the column, and the columns were eluted with MeOH (4 mL). The free base of the amine was released by eluting the columns with
- 10    triethylamine in MeOH (1N). These eluants were concentrated *in vacuo* and treated with a solution of triethylamine in 1:1 toluene: acetonitrile (0.83 mM, 0.15 mL). Next, a solution of **C32** (16.3 mg, 0.05 mmol) in 1:1 toluene: acetonitrile (0.6 mL) was added and the reactions were heated to 90°C for 8 h. The reactions were then shaken at room temperature for 18 h and an aqueous
- 15    solution of sodium hydroxide (1N, 1.5 mL) and ethyl acetate (2.2 mL) was added. The reactions were vortexed, and the organics were separated and loaded onto SCX SPE columns. The extraction process was repeated two times, followed by a final wash of the column with EtOAc (5 mL). The crude products were released by eluting the columns with a solution of triethylamine
- 20    in MeOH (1N, 6 mL). Solvent was removed *in vacuo*, and the residues were dissolved in DMSO (1 mL) and purified by one of the following preparative HPLC methods. Method 1 (column: XBridge C<sub>18</sub>, 5 μm, 19 x 100 mm; Solvent A: 0.03% ammonium hydroxide in water (v/v); Solvent B: 0.03% ammonium hydroxide in acetonitrile (v/v) using an appropriate gradient); Method 2
- 25    (column: XBridge C<sub>18</sub>, 5 μm, 19 x 100 mm; Solvent A: 0.05% trifluoroacetic acid in water (v/v); Solvent B: 0.05% trifluoroacetic acid in acetonitrile (v/v) using an appropriate gradient); Method 3 (column: Atlantis dC<sub>18</sub>, 5 μm, 19 x 100 mm; Solvent A: 0.05% trifluoroacetic acid in water (v/v); Solvent B: 0.05%

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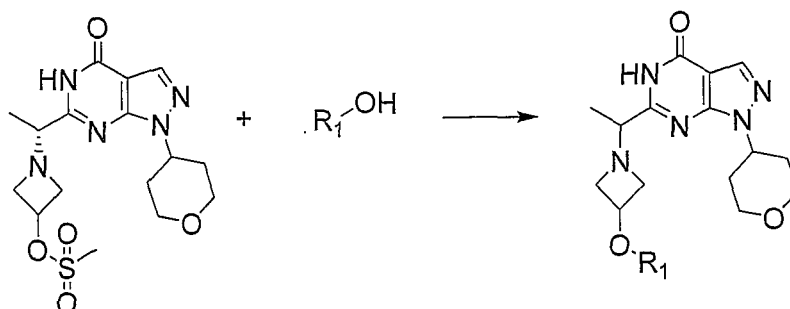
trifluoroacetic acid in acetonitrile (v/v) using an appropriate gradient), to provide the final Examples.

#### Method D

##### Preparation of O-substituted 6-[1-(3-hydroxyazetidin-1-yl)ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-ones



To the alcohols (0.1 mmol) was added 1-[(1R)-1-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]ethyl]azetidin-3-yl methanesulfonate (20 mg, 0.05 mmol) in DMF (0.77 mL). Cesium carbonate (49 mg, 0.15 mmol) was added and the reactions were heated to 70°C for 20 h. The reactions were cooled to room temperature and EtOAc (2 mL) was added, after which the reactions were heated to 35°C and shaken. Reactions were centrifuged to segregate particulates, and 2.4 mL of the reaction mixtures was transferred to SCX-SPE columns. An additional 2.4 mL of EtOAc was added to the reaction vessel, and transferred to the SCX-SPE column. The columns were washed with MeOH (5 mL) and the desired products were then released by eluting with a solution of triethylamine in MeOH (6 mL). The solvent was removed *in vacuo*. A solution of trifluoroacetic acid in dichloromethane (10%, 0.5 mL) was added, and the mixtures were shaken for 15 mins. Solvents were removed *in vacuo* and the crude samples were dissolved in DMSO (0.6 mL) and purified using the conditions described for Method A, to afford the final Examples.

Method EPreparation of O-substituted 6-[1-(3-hydroxyazetidin-1-yl)ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-ones

- 5        The products were synthesized by following the general procedure of Method D, except that 1-[(1*R*)-1-[4-oxo-1-(tetrahydro-2*H*-pyran-4-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl]ethyl]azetidin-3-yl methanesulfonate (20 mg, 0.05 mmol) was dissolved in 0.50 mL of acetonitrile instead of DMF, and potassium carbonate (21 mg, 0.15 mmol) was used in place of cesium carbonate. Compounds were purified using
- 10        the conditions described for Method A, to provide the final Examples.

Table 3

| Ex. No. | Method | IUPAC Name   | Retention Time (min.) | MS: Obs ion (M+1) |
|---------|--------|--|-----------------------|-------------------|
| 88      | A      | 1-cyclopentyl-6-[1-(3-phenylpyrrolidin-1-yl)ethyl]-1,5-dihydro-4H-pyrazolo[3,4- <i>d</i> ]pyrimidin-4-one, trifluoroacetate salt                           | 2.98 <sup>a</sup>     | 378.2             |
| 89      | A      | 6-(1-azetidin-1-ylethyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4- <i>d</i> ]pyrimidin-4-one, trifluoroacetate salt                                       | 2.41 <sup>a</sup>     | 288.2             |
| 90      | A      | 1-cyclopentyl-6-{1-[(3 <i>R</i> )-3-(2-methoxyphenoxy)pyrrolidin-1-yl]ethyl}-1,5-dihydro-4H-pyrazolo[3,4- <i>d</i> ]pyrimidin-4-one, trifluoroacetate salt | 2.96 <sup>a</sup>     | 424.2             |
| 91      | A      | 6-{1-[3-(2-chlorophenyl)pyrrolidin-1-yl]ethyl}-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4- <i>d</i> ]pyrimidin-4-one, trifluoroacetate salt                 | 3.11 <sup>a</sup>     | 412.2             |

| Ex. No. | Method | IUPAC Name   | Retention Time (min.) | MS: Obs ion (M+1) |
|---------|--------|--|-----------------------|-------------------|
| 92      | A      | 1-cyclopentyl-6-[1-(3-pyridin-4-ylpyrrolidin-1-yl)ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt                                  | 2.33 <sup>a</sup>     | 379.41            |
| 93      | D      | 5-fluoro-2-[(1-{1-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]ethyl}azetidin-3-yl)oxy]benzonitrile, trifluoroacetate salt | 2.57 <sup>a</sup>     | 439.1             |
| 94      | E      | 6-{1-[3-(pyridin-3-yloxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt                | 1.85 <sup>a</sup>     | 397.2             |
| 95      | E      | 2-[(1-{1-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]ethyl}azetidin-3-yl)oxy]benzonitrile, trifluoroacetate salt          | 2.48a                 | 421.2             |
| 96      | E      | 6-{1-[3-(2-chloro-4-methylphenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt       | 2.79a                 | 444.2             |
| 97      | E      | 6-{1-[3-(4-chloro-3-methylphenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt       | 2.87a                 | 444.3             |
| 98      | D      | 6-{1-[3-(isoquinolin-5-yloxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt            | 2.06a                 | 447.2             |
| 99      | D      | 6-{1-[3-(2,6-difluorophenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt            | 2.54a                 | 432.1             |
| 100     | D      | 6-{1-[3-(3-chloro-4-fluorophenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,                             | 2.77a                 | 448               |

| Ex. No. | Method | IUPAC Name   | Retention Time (min.) | MS: Obs ion (M+1) |
|---------|--------|--|-----------------------|-------------------|
|         |        | trifluoroacetate salt  |                       |                   |
| 101     | D      | 6-{1-[3-(2-chloro-3,4-difluorophenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt   | 2.82a                 | 466               |
| 102     | D      | 6-{1-[3-(4-chloro-2-methylphenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt       | 2.88a                 | 444.1             |
| 103     | D      | 6-{1-[3-(2,5-dichlorophenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt            | 2.81a                 | 464               |
| 104     | D      | 3-fluoro-4-[(1-{1-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]ethyl}azetidin-3-yl)oxy]benzonitrile, trifluoroacetate salt | 2.57a                 | 437.9             |
| 105     | D      | 3-chloro-4-[(1-{1-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]ethyl}azetidin-3-yl)oxy]benzonitrile, trifluoroacetate salt | 2.62a                 | 455.1             |
| 106     | D      | 6-{1-[3-(quinolin-7-yloxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt               | 2.12a                 | 447.1             |
| 107     | D      | 6-{1-[3-(2,3-difluoro-4-methylphenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt   | 2.79a                 | 446.1             |
| 108     | D      | 6-{1-[3-(2-chlorophenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate                     | 2.67a                 | 430               |

| Ex. No. | Method | IUPAC Name  | Retention Time (min.) | MS: Obs ion (M+1) |
|---------|--------|---|-----------------------|-------------------|
|         |        | salt  |                       |                   |
| 109     | D      | 2-chloro-3-fluoro-6-[(1-{1-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]ethyl}azetidin-3-yl)oxy]benzonitrile, trifluoroacetate salt | 2.76a                 | 473.1             |
| 110     | D      | 6-{1-[3-(2-fluorophenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt                         | 2.53a                 | 414.1             |
| 111     | D      | 6-{1-[3-(2-chloro-5-methoxyphenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt               | 2.72a                 | 460.1             |
| 112     | D      | 6-{1-[3-(isoquinolin-7-yloxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt                     | 2.11a                 | 447.1             |
| 113     | D      | 6-{1-[3-(4-chlorophenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt                         | 2.73a                 | 430.1             |
| 114     | D      | 6-{1-[3-(3-chlorophenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt                         | 2.73a                 | 430.1             |
| 115     | D      | 6-{1-[3-(3,5-difluorophenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt                     | 2.68a                 | 432.1             |
| 116     | D      | 6-{1-[3-(2-fluoro-5-methylphenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,                                      | 2.71a                 | 428.1             |

| Ex. No. | Method | IUPAC Name  | Retention Time (min.) | MS: Obs ion (M+1) |
|---------|--------|---|-----------------------|-------------------|
|         |        | trifluoroacetate salt   |                       |                   |
| 117     | D      | 6-{1-[3-(4-tert-butylphenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt                         | 3.06a                 | 452.2             |
| 118     | D      | 6-(1-{3-[(7-chloroquinolin-4-yl)oxy]azetidin-1-yl}ethyl)-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt                  | 2.47a                 | 481               |
| 119     | D      | 6-{1-[3-(3-chloro-2-fluorophenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt                    | 2.76a                 | 448               |
| 120     | D      | 6-(1-{3-[(4-fluoro-2,3-dihydro-1-benzofuran-7-yl)oxy]azetidin-1-yl}ethyl)-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt | 2.64a                 | 456.1             |
| 121     | D      | 6-{1-[3-(2-chloro-6-fluorophenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt                    | 2.64a                 | 448.1             |
| 122     | D      | 1-(tetrahydro-2H-pyran-4-yl)-6-(1-{3-[4-(trifluoromethyl)phenoxy]azetidin-1-yl}ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt                  | 2.87a                 | 464.1             |
| 123     | D      | 6-{1-[3-(2,4-difluorophenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt                         | 2.63a                 | 432.1             |
| 124     | D      | 6-{1-[3-(2-chloro-4,5-difluorophenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,                                      | 2.79a                 | 466               |



| Ex. No. | Method | IUPAC Name  | Retention Time (min.) | MS: Obs ion (M+1) |
|---------|--------|---|-----------------------|-------------------|
|         |        | trifluoroacetate salt   |                       |                   |
| 125     | D      | 1-(tetrahydro-2H-pyran-4-yl)-6-(1-{3-[3-(trifluoromethyl)phenoxy]azetidin-1-yl}ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt              | 2.84a                 | 464.1             |
| 126     | D      | 6-{1-[3-(2,5-difluorophenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt                     | 2.61a                 | 432.1             |
| 127     | D      | 1-(tetrahydro-2H-pyran-4-yl)-6-{1-[3-(2,3,4-trifluorophenoxy)azetidin-1-yl]ethyl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt                  | 2.73a                 | 450               |
| 128     | D      | 6-{1-[3-(2-chloro-4-fluorophenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt                | 2.73a                 | 448               |
| 129     | D      | 5-chloro-2-[(1-{1-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]ethyl}azetidin-3-yl)oxy]benzonitrile, trifluoroacetate salt          | 2.7a                  | 455.1             |
| 130     | D      | 2-chloro-6-fluoro-3-[(1-{1-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]ethyl}azetidin-3-yl)oxy]benzonitrile, trifluoroacetate salt | 2.72a                 | 473.1             |
| 131     | D      | 6-{1-[3-(2,3-dichlorophenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt                     | 2.83a                 | 464               |
| 132     | D      | 1-(tetrahydro-2H-pyran-4-yl)-6-(1-{3-[3-(trifluoromethoxy)phenoxy]azetidin-1-yl}ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one,                                   | 2.91a                 | 480.1             |

| Ex. No. | Method | IUPAC Name   | Retention Time (min.) | MS: Obs ion (M+1) |
|---------|--------|--|-----------------------|-------------------|
|         |        | trifluoroacetate salt  |                       |                   |
| 133     | D      | 1-(tetrahydro-2H-pyran-4-yl)-6-{1-[3-(3,4,5-trifluorophenoxy)azetidin-1-yl]ethyl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt       | 2.76a                 | 450               |
| 134     | D      | 1-(tetrahydro-2H-pyran-4-yl)-6-{1-[3-(2,4,5-trifluorophenoxy)azetidin-1-yl]ethyl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt       | 2.68a                 | 450.1             |
| 135     | D      | 6-{1-[3-(4-chloro-2-fluorophenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt     | 2.76a                 | 448               |
| 136     | D      | 6-{1-[3-(5-fluoro-2-methylphenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt     | 2.75a                 | 428.1             |
| 137     | D      | 6-{1-[3-(3-fluoro-5-methoxyphenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt    | 2.7a                  | 444.1             |
| 138     | D      | 6-{1-[3-(3,4-difluoro-2-methylphenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt | 2.82a                 | 446.1             |
| 139     | D      | 6-{1-[3-(2-chloro-6-methylphenoxy)azetidin-1-yl]ethyl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, trifluoroacetate salt     | 2.76a                 | 444               |
| 140     | B      | (3aR,9bR)-2-[(1R)-1-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)ethyl]-1,2,3,3a,5,9b-hexahydro-4H-pyrrolo[3,4-                         | 2.51b                 | 419.1             |

| Ex. No. | Method | IUPAC Name  | Retention Time (min.) | MS: Obs ion (M+1) |
|---------|--------|---|-----------------------|-------------------|
|         |        | c]quinolin-4-one  |                       |                   |
| 141     | B      | 6-((1R)-1-[3-(6-bromopyridin-2-yl)pyrrolidin-1-yl]ethyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one  | 3.06e                 | 457               |
| 142     | B      | (3aR,9bR)-8-chloro-2-((1R)-1-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)ethyl)-1,2,3,3a,5,9b-hexahydro-4H-pyrrolo[3,4-c]quinolin-4-one | 2.57b                 | 453               |
| 143     | C      | 1-cyclopentyl-6-((1R)-1-(3-phenylpyrrolidin-1-yl)ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one   | 2.28c                 | 378.2             |
| 144     | C      | 1-cyclopentyl-6-((1R)-1-[3-(2,3-dimethoxyphenyl)pyrrolidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one  | 2.33c                 | 438.2             |
| 145     | C      | 4-((1-((1R)-1-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)ethyl)azetidin-3-yl)oxy)benzonitrile  | 2.15c                 | 405.1             |
| 146     | C      | 1-cyclopentyl-6-((1R)-1-[3-(3-methylphenoxy)azetidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one  | 2.39c                 | 394.2             |
| 147     | C      | 1-cyclopentyl-6-((1R)-1-[3-(3-methoxyphenoxy)azetidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one   | 2.29c                 | 410.2             |
| 148     | C      | 1-cyclopentyl-6-((1R)-1-[3-(3-methoxyphenyl)-3-methylpyrrolidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                                     | 2.39c                 | 422.2             |
| 149     | C      | 6-((1R)-1-[3-(2-chlorophenyl)pyrrolidin-1-yl]ethyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one   | 2.42c                 | 412.1             |
| 150     | C      | 1-cyclopentyl-6-((1R)-1-[3-(2-fluorophenyl)pyrrolidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one   | 2.31c                 | 396.1             |

| Ex. No. | Method | IUPAC Name  | Retention Time (min.) | MS: Obs ion (M+1) |
|---------|--------|---|-----------------------|-------------------|
| 151     | C      | 1-cyclopentyl-6-[(1R)-1-[3-(4-fluorophenyl)pyrrolidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one             | 2.35c                 | 396.1             |
| 152     | C      | 6-[(1R)-1-[3-(3-chlorophenyl)pyrrolidin-1-yl]ethyl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one             | 2.46c                 | 412.1             |
| 153     | C      | 1-cyclopentyl-6-[(1R)-1-(3-pyridin-4-ylpyrrolidin-1-yl)ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                 | 1.47c                 | 379.1             |
| 154     | C      | 1-cyclopentyl-6-[(1R)-1-[(3R)-3-(2-methylphenoxy)pyrrolidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one       | 2.45c                 | 408.2             |
| 155     | C      | 6-[(1R)-1-[3-(3-chlorophenoxy)azetidin-1-yl]ethyl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one              | 2.44c                 | 414               |
| 156     | C      | 6-[(1S)-1-[(3R)-3-(2-chlorophenoxy)pyrrolidin-1-yl]ethyl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one       | 2.41c                 | 428.1             |
| 157     | C      | 1-cyclopentyl-6-[(1R)-1-[3-(pyridin-3-yloxy)azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one              | 1.5c                  | 381.1             |
| 158     | C      | 1-cyclopentyl-6-[(1R)-1-[3-(2,5-dichlorophenoxy)azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one          | 2.52c                 | 448.1             |
| 159     | C      | 4-{1-[(1R)-1-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)ethyl]pyrrolidin-3-yl}-N,N-dimethylbenzamide | 1.92c                 | 449.2             |
| 160     | C      | 1-cyclopentyl-6-[(1R)-1-[3-(2,5-dimethoxyphenyl)pyrrolidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one        | 2.38c                 | 438.2             |
| 161     | C      | 1-cyclopentyl-6-[(1R)-1-[(3R)-3-(2-methoxyphenoxy)pyrrolidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one      | 2.24c                 | 424.1             |

| Ex. No. | Method | IUPAC Name  | Retention Time (min.) | MS: Obs ion (M+1) |
|---------|--------|---|-----------------------|-------------------|
| 162     | C      | 6-[(1R)-1-(3-benzylazetidin-1-yl)ethyl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one   | 2.31c                 | 378.2             |
| 163     | C      | N-cyclobutyl-3-{1-[(1R)-1-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)ethyl]pyrrolidin-3-yl}benzamide                   | 2.24c                 | 475.2             |
| 164     | C      | 1-cyclopentyl-6-[(1R)-1-[3-(3,4-difluorophenoxy)azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                            | 2.28d                 | 416.1             |
| 165     | C      | 6-[(1R)-1-[3-(4-chlorophenoxy)azetidin-1-yl]ethyl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                                | 2.35d                 | 414.1             |
| 166     | C      | 1-cyclopentyl-6-[(1R)-1-[3-(4-methoxyphenoxy)azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                               | 2.13d                 | 410.1             |
| 167     | C      | 1-cyclopentyl-6-[(1R)-1-[(3S)-3-(2-methoxyphenoxy)pyrrolidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                        | 2.13d                 | 424.1             |
| 168     | C      | 2-[(3R)-1-[(1R)-1-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)ethyl]pyrrolidin-3-yl]oxybenzonitrile                     | 2.1d                  | 419.1             |
| 169     | C      | 1-cyclopentyl-6-[(1R)-1-[3-[4-(trifluoromethyl)phenoxy]azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                     | 2.47d                 | 448.1             |
| 170     | C      | methyl (3R,4S)-1-[(1R)-1-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)ethyl]-4-(4-fluorophenyl)pyrrolidine-3-carboxylate | 2.37c                 | 454.1             |
| 171     | C      | 1-cyclopentyl-6-[(1R)-1-[(3S,4R)-3-methoxy-4-phenylpyrrolidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                       | 2.32c                 | 408.2             |
| 172     | C      | 1-cyclopentyl-6-[(1R)-1-[3-[3-(trifluoromethyl)phenoxy]azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one                     | 2.55c                 | 448.1             |

| Ex. No. | Method | IUPAC Name  | Retention Time (min.) | MS: Obs ion (M+1) |
|---------|--------|---|-----------------------|-------------------|
| 173     | C      | 6-[(1R)-1-[3-(2-chloro-5-fluorophenoxy)azetidin-1-yl]ethyl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one     | 2.43c                 | 432.2             |
| 174     | C      | 1-[(1R)-1-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)ethyl]spiro[azetidine-3,2'-chromen]-4'(3'H)-one | 2.15c                 | 420.1             |
| 175     | C      | 1-cyclopentyl-6-[(1R)-1-[3-(4-fluorophenoxy)azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one              | 2.3c                  | 398.1             |

<sup>a</sup>Column: Waters Xterra MS C18 3.0x50mm, 5  $\mu$ m; Mobile phase A: 0.1% TFA in water

(v/v); Mobile phase B: Acetonitrile; flow rate 1.6 mL/min

| Gradient:   |      |
|-------------|------|
| 0 minutes   | 5%B  |
| 0.1 minutes | 5%B  |
| 5.0 minutes | 95%B |
| 6.0 minutes | 95%B |

5 <sup>b</sup>Column: Xbridge Phenyl 4.6x50mm, 5  $\mu$ m; Mobile phase A: 0.03% NH<sub>4</sub>OH in water (v/v); Mobile phase B: 0.03% NH<sub>4</sub>OH in acetonitrile (v/v); Flow rate 2mL/min

| Gradient: |       |
|-----------|-------|
| 0 minutes | 5% B  |
| 4 minutes | 95%B  |
| 5 minutes | 95% B |

<sup>c</sup>Column: Atlantis dC18 4.6x50mm, 5  $\mu$ m; Mobile phase A: 0.1% TFA in water (v/v); Mobile phase B: 100% acetonitrile; flow rate 2mL/min

| Gradient: |       |
|-----------|-------|
| 0 minutes | 5% B  |
| 4 minutes | 95% B |
| 5 minutes | 95% B |

<sup>d</sup>Column: Symmetry C8 4.6x50mm, 5  $\mu$ m; Mobile phase A: 0.1% TFA in water (v/v); Mobile phase B: 100% acetonitrile; flow rate 2mL/min

| Gradient:   |       |
|-------------|-------|
| 0 minutes   | 5% B  |
| 4.0 minutes | 80% B |
| 5.0 minutes | 80% B |

<sup>e</sup>Column: Symmetry C8 4.6x50mm, 5  $\mu$ m; Mobile phase A: 0.03% NH<sub>4</sub>OH in water (v/v); Mobile phase B: 0.03% NH<sub>4</sub>OH in acetonitrile (v/v); flow rate 2mL/min

| Gradient:   |       |
|-------------|-------|
| 0 minutes   | 5% B  |
| 4.0 minutes | 95% B |
| 5.0 minutes | 95% B |

5

### BIOLOGICAL PROTOCOLS

The utility of the compounds of Formula (I), and the pharmaceutically acceptable salts thereof, in the treatment or prevention of diseases (such as are detailed herein) in mammals (e.g., humans) may be demonstrated by the activity thereof in conventional assays known to one of ordinary skill in the art, including the assays described below. Such assays also provide a means whereby the activities of the compounds of Formula (I) can be compared with the activities of other known compounds.

#### Phosphodiesterase 9 (PDE9) inhibitory activity

PDE9 IC<sub>50</sub>, 384-well assay: Test compounds were solubilized in 100% dimethyl sulfoxide and diluted to the required concentrations in 15% dimethyl sulfoxide/water. The PDE9A enzyme was thawed slowly and diluted in 50mM Tris HCl buffer (pH 7.5 at room temperature) containing 1.3 mM MgCl<sub>2</sub>. Incubations were initiated by the addition of PDE9A enzyme to 384-well plates containing test drugs and radioligand (50nM <sup>3</sup>H-cGMP). After a thirty minute incubation at room temperature, 10  $\mu$ M 6-benzyl-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one was added to each well of the plate to stop the reaction. Phosphodiesterase SPA beads (Amersham/GE) were then added to the assay plate at a concentration of 0.2 mg/well. Activity of test compounds

was assessed by measuring the amount of  $^3\text{H}$ -5'GMP resulting from enzyme cleavage of  $^3\text{H}$ -cGMP radioligand. Levels of  $^3\text{H}$ -5'GMP bound to SPA beads were determined by paralux counting of the assay plates in a Microbeta Trilux Counter (PerkinElmer). Non-specific binding was determined by radioligand  
5 binding in the presence of a saturating concentration of 6-benzyl-1-cyclopentyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (10  $\mu\text{M}$ ). The  $\text{IC}_{50}$  value of each test compound (concentration at which 50% inhibition of specific binding occurs) was calculated by non-linear regression (curve fitting) of the concentration-response and is shown in Table 4 below.

10 PDE9  $\text{IC}_{50}$ , 96-well assay: The assay was performed using the Phosphodiesterase Scintillation Proximity (SPA) assay (GE Healthcare Life Sciences). The assay was carried out in 96 well clear bottom microtiter plates (Costar 3632, Corning Inc). The human recombinant PDE9 enzyme was generated in SF-9 cells, the cell pellets were sonicated in buffer (20 mM Tris,  
15 2mM benzamidine, 1mM EDTA, 250mM sucrose, 100 $\mu\text{M}$  PMSF, pH 7.5 with HCl), centrifuged at 40,000 x g for 20 min at 4°C. The supernatants were stored at -80°C. [ $^3\text{H}$ ]guanosine 3',5'-cyclic phosphate (TRK 392, GE Healthcare Life Sciences) was diluted in assay buffer (50 mM Tris-HCl, pH7.5, containing 1.3 mM  $\text{MgCl}_2$ ) such that the final well concentration was 50 nM.  
20 Test compounds were dissolved in DMSO, diluted in DI  $\text{H}_2\text{O}$  and serially diluted in 20% DMSO/80%  $\text{H}_2\text{O}$ , for a final concentration of 2% DMSO. For the assay the PDE9 was diluted with assay buffer such that 20% or less of the substrate was hydrolyzed to 5'GMP. Each assay well contained 10  $\mu\text{L}$  of test compound or solvent, 40  $\mu\text{L}$  of [ $^3\text{H}$ ]cGMP and 50  $\mu\text{L}$  of enzyme, background  
25 was determined by a high concentration of a PDE inhibitor. The assay was initiated with the addition of the enzyme and carried out at room temperature for 30 min. The assay was terminated with the addition of 10  $\mu\text{L}$  of a PDE9 inhibitor that was sufficient to totally inhibit the enzyme activity, immediately followed by the addition of 50  $\mu\text{L}$  per well of SPA beads. The plates were  
30 sealed, vortexed, allowed to set for >300 min, then counted in a Wallac TriLux



MicroBeta LSC. The IC<sub>50</sub> value of each test compound is shown in Table 4 below.

Table 4

| Ex. No. | PDE9 IC <sub>50</sub> , 384-well assay (μM) | PDE9 IC <sub>50</sub> , 96-well assay (μM) | Ex. No. | PDE9 IC <sub>50</sub> , 384-well assay (μM) | PDE9 IC <sub>50</sub> , 96-well assay (μM) | Ex. No. | PDE9 IC <sub>50</sub> , 384-well assay (μM) | PDE9 IC <sub>50</sub> , 96-well assay (μM) |
|---------|---|--|---------|---|--|---------|---|--|
| 1       | 0.0866                                      | N.D.                                       | 60      | 0.0332*                                     | N.D.                                       | 118     | N.D.  | 0.0404                                     |
| 2       | 0.00971*                                    | N.D.                                       | 61      | N.D.  | 0.0245*                                    | 119     | N.D.  | 0.0449                                     |
| 3       | N.D.  | 0.0373*                                    | 62      | N.D.  | 0.0165*                                    | 120     | N.D.  | 0.0701                                     |
| 4       | N.D.  | 0.0817                                     | 63      | N.D.  | 0.0429                                     | 121     | N.D.  | 0.0911                                     |
| 5       | N.D.  | 0.02                                       | 64      | N.D.  | 0.245                                      | 122     | N.D.  | 0.107                                      |
| 6       | 0.0324*                                     | N.D.                                       | 65      | N.D.  | 0.256                                      | 123     | N.D.  | 0.211                                      |
| 7       | 0.00224*                                    | N.D.                                       | 66      | N.D.  | 0.216                                      | 124     | N.D.  | 0.0646                                     |
| 8       | 0.00933*                                    | N.D.                                       | 67      | 0.0735*                                     | 0.0399*                                    | 125     | N.D.  | 0.0436                                     |
| 9       | 0.01218*                                    | 0.0107                                     | 68      | 0.00847*                                    | 0.00294*                                   | 126     | N.D.  | 0.0574                                     |
| 10      | 0.0202*                                     | N.D.                                       | 69      | N.D.  | 0.0453                                     | 127     | N.D.  | 0.11                                       |
| 11      | 0.0254*                                     | 0.0824                                     | 70      | N.D.  | 0.0572                                     | 128     | N.D.  | 0.0745                                     |
| 12      | 0.0404*                                     | N.D.                                       | 71      | N.D.  | 0.00463                                    | 129     | N.D.  | 0.0447                                     |
| 13      | N.D.  | 0.00949                                    | 72      | N.D.  | 0.0228                                     | 130     | N.D.  | 0.0362                                     |
| 14      | N.D.  | 0.136                                      | 73      | N.D.  | 0.0594                                     | 131     | N.D.  | 0.0223                                     |
| 15      | N.D.  | 0.211                                      | 74      | N.D.  | 0.00745                                    | 132     | N.D.  | 0.0489                                     |
| 16      | N.D.  | 0.047*                                     | 75      | N.D.  | 0.0202                                     | 133     | N.D.  | 0.0514                                     |
| 17      | N.D.  | 0.0156*                                    | 76      | N.D.  | 0.0138                                     | 134     | N.D.  | 0.102                                      |
| 18      | 0.0503*                                     | N.D.                                       | 77      | N.D.  | 0.0272*                                    | 135     | N.D.  | 0.0991                                     |
| 19      | 0.0418*                                     | N.D.                                       | 78      | N.D.  | 0.00541                                    | 136     | N.D.  | 0.119                                      |
| 20      | 0.0274*                                     | N.D.                                       | 79      | N.D.  | 0.00456                                    | 137     | N.D.  | 0.0324                                     |
| 21      | 0.0437*                                     | N.D.                                       | 80      | N.D.  | 0.00381*                                   | 138     | N.D.  | 0.0787                                     |
| 22      | 0.0419*                                     | N.D.                                       | 81      | N.D.  | 0.0892                                     | 139     | N.D.  | 0.215                                      |
| 23      | 0.0282*                                     | N.D.                                       | 82      | N.D.  | 0.0503                                     | 140     | 0.292                                       | N.D.                                       |
| 24      | 0.0343*                                     | N.D.                                       | 83      | 0.0132*                                     | 0.0314                                     | 141     | 0.0617                                      | N.D.                                       |
| 25      | 0.043*                                      | N.D.                                       | 84      | N.D.  | 0.0132                                     | 142     | 0.763                                       | N.D.                                       |

| Ex. No. | PDE9<br>IC <sub>50</sub> ,<br>384-well<br>assay<br>( $\mu$ M) | PDE9<br>IC <sub>50</sub> , 96-<br>well<br>assay<br>( $\mu$ M) | Ex. No. | PDE9<br>IC <sub>50</sub> ,<br>384-well<br>assay<br>( $\mu$ M) | PDE9<br>IC <sub>50</sub> , 96-<br>well<br>assay<br>( $\mu$ M) | Ex. No. | PDE9<br>IC <sub>50</sub> ,<br>384-<br>well<br>assay<br>( $\mu$ M) | PDE9<br>IC <sub>50</sub> ,<br>96-<br>well<br>assay<br>( $\mu$ M) |
|---------|---|---|---------|---|---|---------|---|--|
| 26      | 0.0319*   | N.D.  | 85      | N.D.  | 0.0348*   | 143     | 0.273   | N.D.   |
| 27      | 0.0539*   | N.D.  | 86      | N.D.  | 0.0241*   | 144     | 0.0729  | N.D.   |
| 28      | 0.0424*   | N.D.  | 87      | 0.0555*   | N.D.  | 145     | 0.0248*   | N.D.   |
| 29      | 0.0633*   | N.D.  | 88      | N.D.  | 0.23*   | 146     | 0.0572*   | N.D.   |
| 30      | 0.0596*   | N.D.  | 89      | N.D.  | 0.593*  | 147     | 0.0243*   | N.D.   |
| 31      | 0.0127*   | N.D.  | 90      | N.D.  | 0.211*  | 148     | 0.568   | N.D.   |
| 32      | 0.0219*   | N.D.  | 91      | N.D.  | 0.148*  | 149     | 0.321   | N.D.   |
| 33      | 0.0127*   | N.D.  | 92      | N.D.  | 0.382*  | 150     | 0.517*  | N.D.   |
| 34      | 0.00781*  | N.D.  | 93      | N.D.  | 0.0694  | 151     | 0.41  | N.D.   |
| 35      | 0.169*  | N.D.  | 94      | N.D.  | 0.31  | 152     | 0.35  | N.D.   |
| 36      | 0.237*  | N.D.  | 95      | N.D.  | 0.0283  | 153     | 0.174   | N.D.   |
| 37      | N.D.  | 0.032   | 96      | N.D.  | 0.0142  | 154     | 0.661   | N.D.   |
| 38      | 0.0225*   | 0.0125*   | 97      | N.D.  | 0.0233  | 155     | 0.155   | N.D.   |
| 39      | 0.0298*   | N.D.  | 98      | N.D.  | 0.0156  | 156     | 0.292   | N.D.   |
| 40      | 0.066*  | N.D.  | 99      | N.D.  | 0.112   | 157     | 0.0289*   | N.D.   |
| 41      | 0.0518*   | N.D.  | 100     | N.D.  | 0.0638  | 158     | 0.248*  | N.D.   |
| 42      | 0.0325*   | N.D.  | 101     | N.D.  | 0.0488  | 159     | 0.332   | N.D.   |
| 43      | 0.0146*   | N.D.  | 102     | N.D.  | 0.0845  | 160     | 0.151   | N.D.   |
| 44      | 0.0851*   | N.D.  | 103     | N.D.  | 0.0309  | 161     | 0.216   | N.D.   |
| 45      | 0.18*   | N.D.  | 104     | N.D.  | 0.0332  | 162     | 0.0348*   | N.D.   |
| 46      | 0.025*  | N.D.  | 105     | N.D.  | 0.0426  | 163     | 0.0533*   | N.D.   |
| 47      | 0.0312*   | N.D.  | 106     | N.D.  | 0.0214  | 164     | 0.125   | N.D.   |
| 48      | 0.0186*   | N.D.  | 107     | N.D.  | 0.0472  | 165     | 0.184   | N.D.   |
| 49      | 0.0198*   | N.D.  | 108     | N.D.  | 0.0521  | 166     | 0.0172*   | N.D.   |
| 50      | 0.0105*   | N.D.  | 109     | N.D.  | 0.0301  | 167     | 0.915   | N.D.   |
| 51      | 0.0115*   | N.D.  | 110     | N.D.  | 0.148   | 168     | 0.336   | N.D.   |
| 52      | 0.032*  | N.D.  | 111     | N.D.  | 0.0344  | 169     | 0.713   | N.D.   |
| 53      | 0.0258*   | N.D.  | 112     | N.D.  | 0.0583  | 170     | 0.693   | N.D.   |
| 54      | N.D.  | 0.0702  | 113     | N.D.  | 0.0882  | 171     | 0.913   | N.D.   |
| 55      | N.D.  | 0.0211*   | 114     | N.D.  | 0.0856  | 172     | 0.335   | N.D.   |

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| Ex.<br>No. | PDE9<br>IC <sub>50</sub> ,<br>384-well<br>assay<br>( $\mu$ M) | PDE9<br>IC <sub>50</sub> , 96-<br>well<br>assay<br>( $\mu$ M) | Ex.<br>No.      | PDE9<br>IC <sub>50</sub> ,<br>384-well<br>assay<br>( $\mu$ M) | PDE9<br>IC <sub>50</sub> , 96-<br>well<br>assay<br>( $\mu$ M) | Ex.<br>No. | PDE9<br>IC <sub>50</sub> ,<br>384-<br>well<br>assay<br>( $\mu$ M) | PDE9<br>IC <sub>50</sub> ,<br>96-<br>well<br>assay<br>( $\mu$ M) |
|------------|---|---|-----------------|---|---|------------|---|--|
| 56         | N.D.  | 0.00537*  | 115             | N.D.  | 0.0404  | 173        | 0.153   | N.D.   |
| 57         | 0.0671*   | 0.222*  | 116             | N.D.  | 0.0908  | 174        | 0.0617  | N.D.   |
| 58         | N.D.  | 0.0225  | 117             | N.D.  | 0.234   | 175        | 0.0612  | N.D.   |
| 59         | N.D.  | 0.0105*   | N.D. = not done |   |   |            |   |  |

\*Value represents the geometric mean of 2-8 IC<sub>50</sub> determinations

All references cited throughout this specification are expressly incorporated herein by reference.

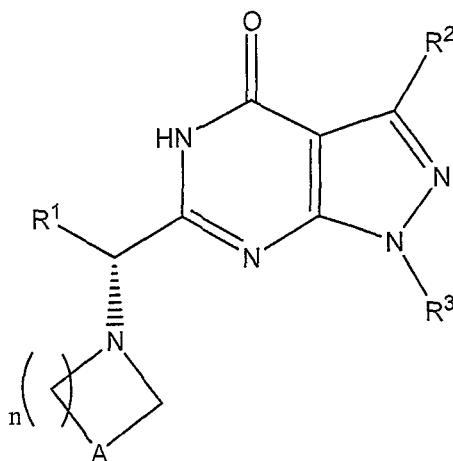
Although certain presently preferred embodiments of the invention have been described herein, it will be apparent to those skilled in the art to which the invention pertains that variations and modifications of the described embodiments may be made without departing from the spirit and scope of the invention. Accordingly, it is intended that the invention be limited only to the extent required by the appended claims and the applicable rules of law.

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**CLAIMS**

We claim:

1. A compound of Formula (I),



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R<sup>1</sup> is selected from the group consisting of

- (i) hydrogen,
- (ii) (C<sub>1</sub>-C<sub>4</sub>)alkyl,
- (iii) (C<sub>2</sub>-C<sub>4</sub>)alkenyl,
- (iv) (C<sub>2</sub>-C<sub>4</sub>)alkynyl,
- (v) (C<sub>1</sub>-C<sub>4</sub>)alkoxy,
- (vi) (C<sub>1</sub>-C<sub>4</sub>)haloalkyl,
- (vii) (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, optionally substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, cyano, carboxy, and carbamoyl,
- (viii) 4 to 10 member heterocycloalkyl, optionally substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, cyano, carboxy, and carbamoyl,
- (ix) aryl, optionally substituted with one to three substituents, the substituents being independently selected from the group

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consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, cyano, carboxy, and carbamoyl, and

- (x) heteroaryl, optionally substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, cyano, carboxy, and carbamoyl;

R<sup>2</sup> is selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, cyano, and (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl;

R<sup>3</sup> is selected from the group consisting of (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>2</sub>-C<sub>6</sub>)alkenyl, (C<sub>2</sub>-C<sub>6</sub>)alkynyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, each of which optionally may be substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, and (C<sub>1</sub>-C<sub>4</sub>)haloalkyl;

n is 1 or 2;

A is -CR<sup>4</sup>R<sup>5</sup>- or -CHR<sup>a</sup>-CHR<sup>b</sup>-;

R<sup>4</sup> is selected from the group consisting of

- (i) hydrogen,
- (ii) (C<sub>1</sub>-C<sub>7</sub>)alkyl,
- (iii) (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl,
- (iv) 4 to 10 member heterocycloalkyl,
- (v) aryl, optionally substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, cyano, carboxy, and carbamoyl,
- (vi) heteroaryl, optionally substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, cyano, carboxy, and carbamoyl, and

(vii) LR<sup>6</sup>, wherein:

L is selected from the group consisting of -CH<sub>2</sub>-, -NR<sup>7</sup>-, and -O-;

5  $R^6$  is aryl, heteroaryl,  $(C_1-C_8)$ alkyl,  $(C_3-C_8)$ cycloalkyl, 4 to 10 member heterocycloalkyl, or  $(C_1-C_8)$ alkoxy, each of which optionally may be substituted with one to three substituents, the substituents being independently selected from the group consisting of  $(C_1-C_4)$ alkyl,  $(C_1-C_4)$ alkoxy, halo,  $(C_1-C_4)$ haloalkyl,  $(C_1-C_4)$ haloalkoxy,  $(C_3-C_6)$ cycloalkyl, cyano, carboxy, and carbamoyl; and

$R^7$  is hydrogen, methyl or ethyl;

10  $R^5$  is selected from the group consisting of hydrogen, hydroxyl,  $(C_1-C_4)$ alkoxy, halogen, and  $(C_1-C_6)$ alkyl; or  $R^4$  and  $R^5$ , together with the carbon to which they are attached, form a cycloalkyl or heterocycloalkyl ring that optionally incorporates an oxo group and is optionally substituted with  $(C_1-C_8)$ alkyl,  $(C_3-C_8)$ cycloalkyl, halo,  $(C_1-C_8)$ alkoxy, or  $(C_1-C_3)$ haloalkyl;

$R^a$  is  $(C_1-C_4)$ alkoxy or  $R^8-O-C(O)-$ , wherein  $R^8$  is  $(C_1-C_4)$ alkyl; and

15  $R^b$  is aryl, heteroaryl, or heterocycloalkyl, optionally substituted with halo,  $(C_1-C_8)$ alkyl,  $(C_3-C_8)$ cycloalkyl,  $(C_1-C_8)$ alkoxy, or  $(C_1-C_3)$ haloalkyl; or  $R^a$  and  $R^b$ , together with the carbons to which they are attached, form a cycloalkyl or heterocycloalkyl ring that optionally incorporates an oxo group and is optionally substituted with  $(C_1-C_8)$ alkyl,  $(C_3-C_8)$ cycloalkyl, halo,  $(C_1-C_8)$ alkoxy, or  $(C_1-C_3)$ haloalkyl.

2. The compound of claim 1, wherein:

$R^1$  is selected from the group consisting of

- 25 (i)  $(C_1-C_4)$ alkyl,  
(ii)  $(C_3-C_6)$ cycloalkyl,  
(iii)  $(C_1-C_4)$ haloalkyl,  
(iv) optionally substituted 4 to 10 member heterocycloalkyl,  
(v) optionally substituted aryl, and  
(vi) optionally substituted heteroaryl;

30  $R^2$  is selected from the group consisting of hydrogen,  $(C_1-C_4)$ alkyl,  $(C_1-C_4)$ haloalkyl, cyano, and cyclopropyl;

$R^4$  is selected from the group consisting of

- (i) hydrogen,
- (ii) aryl, optionally substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, cyano, carboxy, and carbamoyl,
- (iii) heteroaryl, optionally substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, cyano, carboxy, and carbamoyl, and
- (iv) LR<sup>6</sup>, wherein:  
L is selected from the group consisting of -CH<sub>2</sub>-, -NR<sup>7</sup>-, and -O-; and  
R<sup>6</sup> is aryl or heteroaryl, each of which optionally may be substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, cyano, carboxy, and carbamoyl;
- R<sup>5</sup> is selected from the group consisting of hydrogen, hydroxyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, and (C<sub>1</sub>-C<sub>6</sub>)alkyl; or R<sup>4</sup> and R<sup>5</sup>, together with the carbon to which they are attached, form a cyclic ketone; and
- R<sup>b</sup> is aryl or heteroaryl, optionally substituted with halo, (C<sub>1</sub>-C<sub>3</sub>)alkyl, or (C<sub>1</sub>-C<sub>3</sub>)haloalkyl; or R<sup>a</sup> and R<sup>b</sup>, together with the carbons to which they are attached, form a cycloalkyl or heterocycloalkyl ring that optionally incorporates an oxo group and is optionally substituted with (C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, halo, (C<sub>1</sub>-C<sub>8</sub>)alkoxy, or (C<sub>1</sub>-C<sub>3</sub>)haloalkyl.
3. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein:
- R<sup>1</sup> is (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, or phenyl;
- R<sup>2</sup> is hydrogen;
- R<sup>3</sup> is selected from the group consisting of isopropyl, cyclobutyl, cyclopentyl, tetrahydrofuranyl, and tetrahydropyranyl;

A is  $-\text{CR}^4\text{R}^5-$ ; and

L is  $-\text{CH}_2-$  or  $-\text{O}-$ .

4. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein:

5  $\text{R}^1$  is methyl, ethyl, cyclopropyl or phenyl;

$\text{R}^4$  is selected from the group consisting of hydrogen, phenyl, pyridinyl, pyrimidinyl, quinolinyl, pyrazinyl, pyridazinyl, phthalazinyl, quinazolinyl, naphthyridinyl, quinoxalinyl, isoquinolinyl, benzofuranyl, dihydrobenzofuranyl, each of which optionally may be substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, carbamoyl, and  $\text{LR}^6$ ;

$\text{R}^5$  is selected from the group consisting of hydrogen, methyl, hydroxy, and halo; or  $\text{R}^4$  and  $\text{R}^5$ , together with the carbon to which they are attached form benzopyranone; and

15  $\text{R}^6$  is phenyl, pyrimidinyl, pyridinyl, pyrazinyl, quinoxalinyl, phthalazinyl, pyridazinyl, quinazolinyl, naphthyridinyl, isoquinolinyl, quinolinyl, benzofuranyl, each of which optionally may be substituted with one to three substituents, the substituents being independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, halo, (C<sub>1</sub>-C<sub>4</sub>)haloalkyl, (C<sub>1</sub>-C<sub>4</sub>)haloalkoxy, and cyano.

20 5. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein:

$\text{R}^1$  is methyl or ethyl;

n is 1;

$\text{R}^3$  is cyclopentyl or tetrahydro-2H-pyranyl;

25  $\text{R}^4$  is pyrimidinyl or  $\text{LR}^6$ ;

$\text{R}^5$  is hydrogen, methyl, hydroxy, or fluoro;

L is  $-\text{O}-$ ; and

$\text{R}^6$  is optionally substituted phenyl.

30 6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

$\text{R}^1$  is methyl, ethyl, cyclopropyl or phenyl;



$R^2$  is hydrogen;

$R^3$  is selected from the group consisting of isopropyl, cyclobutyl, cyclopentyl, and tetrahydro-2H-pyran-4-yl;

$n$  is 1;

5 A is  $-\text{CHR}^a-\text{CHR}^b-$ ;

$R^a$  is methoxy or  $R^8-\text{O}-\text{C}(\text{O})-$ , wherein  $R^8$  is methyl; and

$R^b$  is phenyl, optionally substituted with halo; or  $R^a$  and  $R^b$ , together with the carbons to which they are attached, form a dihydroquinolone, optionally substituted with halo.

10 7. The compound of claim 1, selected from the group consisting of:  
1-cyclopentyl-6-[(1*R*)-1-(3-pyrimidin-2-ylazetidin-1-yl)ethyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

1-cyclopentyl-6-[(1*R*)-1-[3-(pyrimidin-2-yloxy)azetidin-1-yl]ethyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

15 1-cyclopentyl-6-[(1*R*)-1-(3-pyridin-2-ylazetidin-1-yl)ethyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

1-cyclopentyl-6-[(1*R*)-1-(3-pyridin-4-ylazetidin-1-yl)ethyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

20 1-cyclopentyl-6-[(1*R*)-1-(3-pyridin-3-ylazetidin-1-yl)ethyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

1-cyclopentyl-6-[(1*R*)-1-(3-pyrimidin-5-ylazetidin-1-yl)ethyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

1-cyclopentyl-6-[(1*R*)-1-(3-pyridazin-3-ylazetidin-1-yl)ethyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

25 1-cyclopentyl-6-[(1*R*)-1-[3-(pyrimidin-5-ylmethyl)azetidin-1-yl]ethyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

1-cyclopentyl-6-[(1*R*)-1-(3-pyrimidin-4-ylazetidin-1-yl)ethyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

30 1-cyclopentyl-6-[(1*R*)-1-[3-(2-methylpyrimidin-4-yl)azetidin-1-yl]ethyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

- 1-cyclopentyl-6-[(1R)-1-(3-quinolin-2-ylazetidin-1-yl)ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 1-cyclopentyl-6-[(1R)-1-[(3R)-3-(pyrimidin-2-yloxy)pyrrolidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 5 1-cyclopentyl-6-[(1R)-1-[(3S)-3-(pyrimidin-2-yloxy)pyrrolidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 1-cyclopentyl-6-[(1R)-1-{3-[(6-methylpyridin-3-yl)methyl]azetidin-1-yl}ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 1-cyclopentyl-6-[(1R)-1-(3-pyrimidin-2-ylpyrrolidin-1-yl)ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 10 1-cyclopentyl-6-[(1R)-1-[3-(5-methylpyrimidin-2-yl)azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 1-cyclopentyl-6-[(1R)-1-[3-(5-cyclopropylpyrimidin-2-yl)azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 15 1-cyclopentyl-6-[(1R)-1-[3-(4,6-dimethylpyrimidin-2-yl)azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 1-cyclopentyl-6-[(1R)-1-[3-(4-methylpyrimidin-2-yl)azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 1-cyclopentyl-6-[(1R)-1-[3-(3-fluorobenzyl)azetidin-1-yl]ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 20 (3aR,9bR)-2-[(1R)-1-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)ethyl]-1,2,3,3a,5,9b-hexahydro-4H-pyrrolo[3,4-c]quinolin-4-one;
- 6-[(1R)-1-[3-(6-bromopyridin-2-yl)pyrrolidin-1-yl]ethyl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 25 (3aR,9bR)-8-chloro-2-[(1R)-1-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)ethyl]-1,2,3,3a,5,9b-hexahydro-4H-pyrrolo[3,4-c]quinolin-4-one;
- 1-cyclopentyl-6-[(1R)-1-(3-phenylpyrrolidin-1-yl)ethyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 30

- 1-cyclopentyl-6-((1R)-1-[3-(2,3-dimethoxyphenyl)pyrrolidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 4-((1-[(1R)-1-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)ethyl]azetidin-3-yl)oxy)benzonitrile;
- 5 1-cyclopentyl-6-((1R)-1-[3-(3-methylphenoxy)azetidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 1-cyclopentyl-6-((1R)-1-[3-(3-methoxyphenoxy)azetidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 1-cyclopentyl-6-((1R)-1-[3-(3-methoxyphenyl)-3-methylpyrrolidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 10 6-((1R)-1-[3-(2-chlorophenyl)pyrrolidin-1-yl]ethyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 1-cyclopentyl-6-((1R)-1-[3-(2-fluorophenyl)pyrrolidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 15 1-cyclopentyl-6-((1R)-1-[3-(4-fluorophenyl)pyrrolidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 6-((1R)-1-[3-(3-chlorophenyl)pyrrolidin-1-yl]ethyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 1-cyclopentyl-6-((1R)-1-(3-pyridin-4-ylpyrrolidin-1-yl)ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 20 1-cyclopentyl-6-((1R)-1-[(3R)-3-(2-methylphenoxy)pyrrolidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 6-((1R)-1-[3-(3-chlorophenoxy)azetidin-1-yl]ethyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 25 6-((1S)-1-[(3R)-3-(2-chlorophenoxy)pyrrolidin-1-yl]ethyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 1-cyclopentyl-6-((1R)-1-[3-(pyridin-3-yloxy)azetidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 1-cyclopentyl-6-((1R)-1-[3-(2,5-dichlorophenoxy)azetidin-1-yl]ethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 30

- 4-{1-[(1R)-1-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)ethyl]pyrrolidin-3-yl}-N,N-dimethylbenzamide;  
1-cyclopentyl-6-{(1R)-1-[3-(2,5-dimethoxyphenyl)pyrrolidin-1-yl]ethyl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 5 1-cyclopentyl-6-{(1R)-1-[(3R)-3-(2-methoxyphenoxy)pyrrolidin-1-yl]ethyl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;  
6-{(1R)-1-(3-benzylazetidin-1-yl)ethyl}-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 10 N-cyclobutyl-3-{1-[(1R)-1-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)ethyl]pyrrolidin-3-yl}benzamide;  
1-cyclopentyl-6-{(1R)-1-[3-(3,4-difluorophenoxy)azetidin-1-yl]ethyl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 15 6-{(1R)-1-[3-(4-chlorophenoxy)azetidin-1-yl]ethyl}-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;  
1-cyclopentyl-6-{(1R)-1-[3-(4-methoxyphenoxy)azetidin-1-yl]ethyl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 20 1-cyclopentyl-6-{(1R)-1-[(3S)-3-(2-methoxyphenoxy)pyrrolidin-1-yl]ethyl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;  
2-[(3R)-1-[(1R)-1-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)ethyl]pyrrolidin-3-yl]oxy)benzonitrile;
- 25 1-cyclopentyl-6-{(1R)-1-[3-[4-(trifluoromethyl)phenoxy]azetidin-1-yl]ethyl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;  
methyl(3R,4S)-1-[(1R)-1-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)ethyl]-4-(4-fluorophenyl)pyrrolidine-3-carboxylate;
- 30 1-cyclopentyl-6-{(1R)-1-[(3S,4R)-3-methoxy-4-phenylpyrrolidin-1-yl]ethyl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;  
1-cyclopentyl-6-{(1R)-1-[3-[3-(trifluoromethyl)phenoxy]azetidin-1-yl]ethyl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;  
6-{(1R)-1-[3-(2-chloro-5-fluorophenoxy)azetidin-1-yl]ethyl}-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-[(1*R*)-1-(1-cyclopentyl-4-oxo-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl)ethyl]spiro[azetidine-3,2'-chromen]-4'(3'*H*)-one;

1-cyclopentyl-6-[(1*R*)-1-[3-(4-fluorophenoxy)azetidin-1-yl]ethyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

5 or a pharmaceutically acceptable salt thereof.

8. The compound of claim 1, selected from the group consisting of:

6-[(1*R*)-1-[3-(4-methylpyridin-2-yl)azetidin-1-yl]ethyl]-1-(tetrahydro-2*H*-pyran-4-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

6-[cyclopropyl(3-phenoxyazetidin-1-yl)methyl]-1-(tetrahydro-2*H*-pyran-4-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

2-fluoro-5-[(1-{1-[4-oxo-1-(tetrahydro-2*H*-pyran-4-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-6-yl]ethyl}azetidin-3-yl)oxy]benzonitrile;

6-[(1*R*)-1-(3-quinolin-2-ylazetidin-1-yl)ethyl]-1-(tetrahydro-2*H*-pyran-4-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

15 6-[(1*R*)-1-[3-(6-methylpyridin-2-yl)azetidin-1-yl]ethyl]-1-(tetrahydro-2*H*-pyran-4-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

6-[(1*R*)-1-[3-(4-fluorophenoxy)azetidin-1-yl]ethyl]-1-(tetrahydro-2*H*-pyran-4-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

20 6-[(1*R*)-1-[3-(5-chloropyrimidin-2-yl)azetidin-1-yl]ethyl]-1-(tetrahydro-2*H*-pyran-4-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

6-[(1*R*)-1-(3-phenylazetidin-1-yl)ethyl]-1-(tetrahydro-2*H*-pyran-4-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

6-[(1*R*)-1-(3-pyrazin-2-ylazetidin-1-yl)ethyl]-1-(tetrahydro-2*H*-pyran-4-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

25 6-[(1*R*)-1-(3-pyrimidin-2-ylazetidin-1-yl)ethyl]-1-(tetrahydro-2*H*-pyran-4-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

6-[(1*R*)-1-(3-pyridin-2-ylazetidin-1-yl)ethyl]-1-(tetrahydro-2*H*-pyran-4-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

30 6-[(1*R*)-1-(3-pyridin-4-ylazetidin-1-yl)ethyl]-1-(tetrahydro-2*H*-pyran-4-yl)-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

- 6-[(1R)-1-(3-pyridin-3-ylazetidin-1-yl)ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 6-[(1R)-1-(3-pyrimidin-5-ylazetidin-1-yl)ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 5 6-[(1R)-1-(3-pyridazin-3-ylazetidin-1-yl)ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 6-[(1R)-1-[3-(2-methylpyrimidin-4-yl)azetidin-1-yl]ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 6-[(1R)-1-[3-(3-fluorobenzyl)azetidin-1-yl]ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 10 6-[(1R)-1-(3-phenoxyazetidin-1-yl)ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 6-[(1R)-1-[3-(6-methylpyridin-2-yl)azetidin-1-yl]propyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 15 6-[(1R)-1-(3-pyridin-2-ylazetidin-1-yl)propyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 6-[(1R)-1-[3-(5-methylpyrimidin-2-yl)azetidin-1-yl]propyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 6-[(1R)-1-[3-(5-chloropyrimidin-2-yl)azetidin-1-yl]propyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 20 6-[(1R)-1-[3-(pyrimidin-2-ylmethyl)azetidin-1-yl]ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 6-[(1R)-1-[3-(5-methylpyrimidin-2-yl)azetidin-1-yl]ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 25 6-[(1R)-1-[3-(5-cyclopropylpyrimidin-2-yl)azetidin-1-yl]ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 6-[(1R)-1-[3-(4,6-dimethylpyrimidin-2-yl)azetidin-1-yl]ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one; and
- 6-[(1R)-1-[3-(4-methylpyrimidin-2-yl)azetidin-1-yl]ethyl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
- 30 or a pharmaceutically acceptable salt thereof.

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9. The compound of claim 1, selected from the group consisting of:  
1-cyclobutyl-6-[(1*R*)-1-[3-(pyrimidin-2-yloxy)azetidin-1-yl]ethyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one; and  
1-isopropyl-6-[1-(3-phenoxyazetidin-1-yl)ethyl]-1,5-dihydro-4*H*-  
5 pyrazolo[3,4-*d*]pyrimidin-4-one;  
or a pharmaceutically acceptable salt thereof.
10. A pharmaceutical composition comprising a compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle, carrier or diluent.
- 10 11. The composition of claim 10, further comprising a second pharmaceutical agent.
12. The composition of claim 11, wherein the second pharmaceutical agent is selected from the group consisting of dimebon, donepezil, galantamine, memantine, rivastigmine, and tacrine.
- 15 13. A method of inhibiting PDE9 in a mammal in need of such inhibition comprising the step of administering to the mammal PDE9-inhibiting amount of:
- a) a compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof; or
- 20 b) a pharmaceutical composition comprising a compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle, carrier or diluent.
14. A method of treating a neurodegenerative disease in a mammal in need of such treatment, comprising the step of administering to the mammal  
25 a therapeutically effective amount of:
- a) a compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof; or
- b) a pharmaceutical composition comprising a compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, and a  
30 pharmaceutically acceptable vehicle, carrier or diluent.

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15. The method of claim 14, wherein the disease is Alzheimer's disease.

16. A method of promoting neurorestoration in a mammal in need of such neurorestoration, comprising the step of administering to the mammal a  
5 therapeutically effective amount of:

a) a compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof; or

b) a pharmaceutical composition comprising a compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, and a  
10 pharmaceutically acceptable vehicle, carrier or diluent.

17. A method of promoting functional recovery in a mammal suffering from an injury of the brain, comprising the step of administering to the mammal a therapeutically effective amount of:

a) a compound of any one of claims 1-9, or a pharmaceutically  
15 acceptable salt thereof; or

b) a pharmaceutical composition comprising a compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle, carrier or diluent.

18. A method of treating cognitive impairment in a mammal in need  
20 of such treatment, comprising the step of administering to the mammal a therapeutically effective amount of:

a) a compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof; or

b) a pharmaceutical composition comprising a compound of any  
25 one of claims 1-9, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle, carrier or diluent.

19. A method of enhancing cognition in a mammal in need of such enhancement comprising the step of administering to the mammal a cognition-enhancing amount of:

a) a compound of any one of claims 1-9, or a pharmaceutically  
30 acceptable salt thereof; or



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b) a pharmaceutical composition comprising a compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle, carrier or diluent.

20. The method of any one of claims 13-19 wherein the mammal is  
5 human.