



(51) International Patent Classification:

C07D 487/04 (2006.01) A61P 13/00 (2006.01)

A61K 31/519 (2006.01) A61P 25/00 (2006.01)

A61P 9/00 (2006.01) A61P 3/00 (2006.01)

(21) International Application Number:

PCT/CN2016/082180

(22) International Filing Date:

16 May 2016 (16.05.2016)

(25) Filing Language:

English

(26) Publication Language:

English

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(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

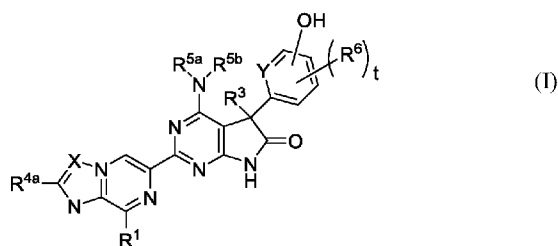
Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

— with international search report (Art. 21(3))

(54) Title: FUSED PYRAZINE DERIVATIVES USEFUL AS SOLUBLE GUANYLATE CYCLASE STIMULATORS



(57) **Abstract:** Provided are certain fused pyrazine compounds of the Formula (I) or a pharmaceutically acceptable salts thereof, wherein X, Y, R¹, R³, R^{4a}, R^{5a}, R^{5b}, R⁶, and the subscript t are described herein. The compounds or their pharmaceutically acceptable salts can modulate the body's production of cyclic guanosine monophosphate ("cGMP"), and are generally suitable for the therapy and prophylaxis of diseases or disorders which are associated with a disturbed cGMP balance. Provided are also pharmaceutical compositions which comprise compounds of Formula (I) or pharmaceutically acceptable salts thereof. Provided are also methods for use of the compounds or their pharmaceutically acceptable salts in the therapy and prophylaxis of the abovementioned diseases and disorders and for preparing pharmaceuticals for this purpose.



FUSED PYRAZINE DERIVATIVES USEFUL AS SOLUBLE GUANYLATE CYCLASE STIMULATORS

5 FIELD OF THE INVENTION

The present invention relates to certain fused pyrazine derivatives of the Formula (I) (also referred to as “compounds of the Formula (I)”, “compounds of Formula (I)”, or “compounds of structural Formula (I)”) pharmaceutical compositions comprising such compounds, and methods of using such compounds for treating diseases or disorders which
10 are associated with a disturbed cyclic guanosine monophosphate (cGMP) balance.

BACKGROUND OF THE INVENTION

cGMP is an important intracellular messenger which triggers a multitude of different effects via the modulation of cGMP-dependent protein kinases, phosphodiesterases and ion
15 channels. Examples are the relaxation of smooth muscles, the inhibition of thrombocyte activation and the inhibition of the proliferation of smooth-muscle cells and of leukocyte adhesion. cGMP is produced by particulate and soluble guanylate cyclases as a response to a number of extracellular and intracellular stimuli. In the case of the particulate guanylate cyclases, stimulation is essentially effected by peptidic messengers, such as the atrial
20 natriuretic peptide or the cerebral natriuretic peptide. The soluble guanylate cyclases (“sGC”), which are cytosolic heterodimeric heme proteins, in contrast, are essentially regulated by a family of low-molecular-weight factors which are formed enzymatically. The most important stimulant is nitrogen monoxide (“NO”) or a closely related species. The function of other factors such as carbon monoxide or the hydroxyl radical is still largely unclear. The binding
25 of NO to the heme with formation of a penta-coordinate heme-nitrosyl complex is proposed as the mechanism of the activation by NO. The associated release of the histidine which is bound in the basal state to the iron converts the enzyme into the active conformation.

Active soluble guanylate cyclases are each composed of an α and a β subunit. Several subunit subtypes have been described which differ from one another with respect to sequence,
30 tissue-specific distribution and expression in different development stages. The subtypes α_1 and β_1 are mainly expressed in brain and lung, while β_2 is found in particular in liver and kidney. The subtype α_2 was shown to be present in human fetal brain. The subunits referred to as α_3 and β_3 were isolated from human brain and are homologous to α_1 and β_1 . More recent works indicate an α_{2i} subunit which contains an insert in the catalytic domain. All

subunits show great homologies in the region of the catalytic domain. The enzymes presumably contain one heme per heterodimer, which is bound via β_1 -Cys-78 and/or β_1 -His-105 and is part of the regulatory center.

Under pathologic conditions, the formation of guanylate-cyclase-activating factors can be reduced, or their degradation may be promoted owing to the increased occurrence of free radicals. The resulting reduced activation of the sGC leads, via a weakening of the respective cGMP-mediated cellular response, for example to an increase of the blood pressure, to platelet activation or to increased cell proliferation and cell adhesion. As a consequence, formation of endothelial dysfunction, atherosclerosis, hypertension, stable or unstable angina pectoris, thrombosis, myocardial infarction, strokes or erectile dysfunction results. Pharmacological stimulation of sGC offers a possibility to normalize cGMP production and therefore may make possible the treatment and/or prevention of such disorders.

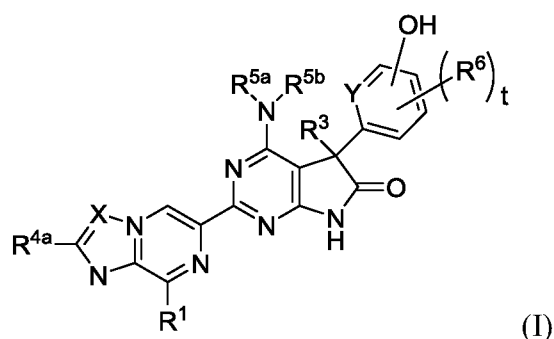
For the pharmacological stimulation of the sGC, use has been made of compounds whose activity is based on an intermediate NO release, for example organic nitrates. The drawback of this treatment is the development of tolerance and a reduction of activity, and the higher dosage which is required because of this.

Various sGC stimulators which do not act via NO release were described by Vesely in a series of publications. However, the compounds, most of which are hormones, plant hormones, vitamins or natural compounds such as, for example, lizard poisons, predominantly only have weak effects on the cGMP formation in cell lysates. D. L. Vesely, Eur. J. Clin. Invest., vol.15, 1985, p. 258; D. L. Vesely, Biochem. Biophys. Res. Comm., vol. 88, 1979, p.1244. A stimulation of heme-free guanylate cyclase by protoporphyrin IX was demonstrated by Ignarro et al., Adv. Pharmacol., vol. 26, 1994, p. 35. Pettibone et al., Eur. J. Pharmacol., vol. 116, 1985 p. 307, described an antihypertensive action of diphenyliodonium hexafluorophosphate and attributed this to a stimulation of sGC. According to Yu et al., Brit. J. Pharmacol., vol. 114, 1995, p.1587, isoliquiritigenin, which has a relaxing action on isolated rat aortas, also activates sGC. Ko et al., Blood vol. 84, 1994, p. 4226, Yu et al., Biochem. J. vol. 306, 1995, p. 787, and Wu et al., Brit. J. Pharmacol. vol. 116, 1995, p. 1973, demonstrated a sGC-stimulating activity of 1-benzyl-3-(5-hydroxymethyl-2-furyl)indazole and demonstrated an antiproliferative and thrombocyte-inhibiting action. Pyrazoles and fused pyrazoles which exhibit a sGC-stimulating activity are described in European Patent No. 908,456 and German Patent Application No. 19,744,027.

It has now been found that the compounds of the present invention effect a strong activation of soluble guanylate cyclase and therefore may be suitable for the therapy and prophylaxis of disorders which are associated with a low cGMP level.

5 SUMMARY OF THE INVENTION

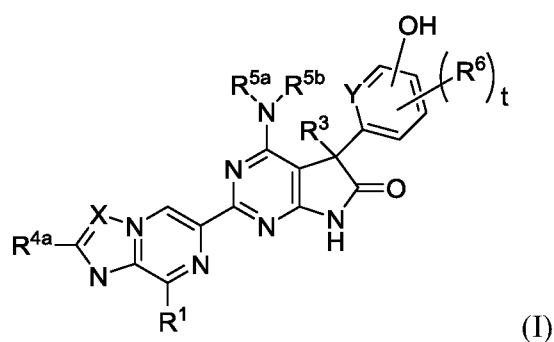
The present invention relates to compounds which activate soluble guanylate cyclase and may be valuable pharmaceutically active compounds for the therapy and prophylaxis of diseases, for example for cardiovascular diseases such as hypertension, heart failure, pulmonary hypertension, angina pectoris, diabetes, cardiac insufficiency, thrombosis, chronic
10 kidney disease, fibrosis or atherosclerosis. The compounds of Formula (I)



are capable of modulating the body's production of cGMP and may be suitable for the therapy and prophylaxis of diseases or disorders which are associated with a disturbed cGMP balance. The invention furthermore relates to processes for preparing compounds of Formula (I), to
15 the use of such compounds for the therapy and prophylaxis of the above mentioned diseases and for preparing compounds for this purpose, and to pharmaceutical compositions which comprise compounds of Formula (I).

DETAILED DESCRIPTION OF THE INVENTION

20 In embodiment no. 1, the present invention provides a compound having structural Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

X is C(R^{4b}) or N;

Y is C(H) or N;

R¹ is:

(a.) (C₁-C₃)alkyl-R²,

5 R² is phenyl, C₃-C₈ cycloalkyl, or C₅-C₇ cycloalkenyl, wherein R² is unsubstituted or substituted by 1 to 3 R^{2a}; each R^{2a} is independently halo, (C₁-C₃)alkyl, or (C₁-C₃)fluoroalkyl;

or

10 (b.) (C₁-C₆)alkyl, wherein said alkyl is unsubstituted or substituted by 1 to 6 fluoro;

R³ is (C₁-C₃)alkyl or (C₃-C₆)cycloalkyl;

R^{4a} is H or (C₁-C₃)alkyl;

R^{4b} is H or NH₂;

15 R^{5a} and R^{5b} are independently H or (C₁-C₆)alkyl, wherein said alkyl is unsubstituted or substituted by 1 to 6 substituents independently selected from fluoro or hydroxyl; or

alternatively, R^{5a} and R^{5b} together with the nitrogen atom to which they are attached form ring C⁵ which is an azetidiny, pyrrolyl, piperidiny, piperazinyl, or azepiny ring, wherein ring C⁵ is unsubstituted or substituted by 1 to 3 substituents which are independently halo, hydroxyl, (C₁-C₃)alkyl, or (C₁-C₃)fluoroalkyl;

each R⁶ is independently halo, (C₁-C₃)alkyl, (C₁-C₃)fluoroalkyl, or cyano; and

the subscript t is 0, 1, 2, or 3; and

with the proviso that the compound is not:

25 4-amino-5-(5-hydroxypyridin-2-yl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidine-6-one;
4-amino-5-(5-hydroxypyridin-2-yl)-5-methyl-2-(8-(4,4,4-trifluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5H-pyrrolo[2,3-*d*]pyrimidine-6(7H)-one; or
30 4-amino-5-cyclopropyl-5-(5-hydroxypyridin-2-yl)-2-(8-(4,4,4-trifluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5H-pyrrolo[2,3-*d*]pyrimidine-6(7H)-one (including pharmaceutically acceptable salts of said three specifically recited compounds).

In embodiment no. 2, the present invention provides the compound having structural Formula (I), wherein X is C(R^{4b}), and the remaining variables are as set forth in embodiment no. 1. In embodiment no. 3, the present invention provides the compound having structural Formula (I), wherein X is C(R^{4b}) and R^{4b} is H, and the remaining variables are as set forth in embodiment no. 1.

In embodiment no. 4, the present invention provides the compound having structural Formula (I), wherein X is N; and the remaining variables are as set forth in embodiment no. 1.

In embodiment no. 5, the present invention provides the compound having structural Formula (I), wherein Y is N, and the remaining variables are as set forth in embodiment no. 1.

In embodiment no. 6, the present invention provides the compound having structural Formula (I), wherein Y is C(H), and the remaining variables are as set forth in embodiment no. 1.

In embodiment no. 7, the present invention provides the compound having structural Formula (I), wherein R¹ is (C₁-C₃)alkyl-R²,

R² is phenyl, C₃-C₈ cycloalkyl, or C₅-C₇ cycloalkenyl, wherein R² is unsubstituted or substituted by 1 to 3 R^{2a}; and each R^{2a} is independently halo, (C₁-C₃)alkyl, or (C₁-C₃)fluoroalkyl; and the remaining variables are as set forth in embodiment no. 1.

In embodiment no. 8, the present invention provides the compound having structural Formula (I), wherein R¹ is -CH₂-R²; R² is as set forth in embodiment no. 7; and the remaining variables are as set forth in embodiment no. 1.

In embodiment no. 9, the present invention provides the compound having structural Formula (I), wherein R¹ is -CH₂-R²; R² is unsubstituted phenyl or phenyl substituted by 1 to 3 R^{2a}; and the remaining variables are as set forth in embodiment no. 1.

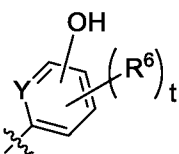
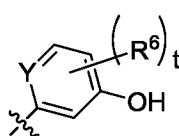
In embodiment no. 10, the present invention provides the compound having structural Formula (I), wherein R³ is methyl, and the remaining variables are as set forth in embodiment no. 1.

In embodiment no. 11, the present invention provides the compound having structural Formula (I), wherein R^{4a} is H, and the remaining variables are as set forth in embodiment no. 1.

In embodiment no. 12, the present invention provides the compound having structural Formula (I), wherein R^{5a} and R^{5b} are H, and the remaining variables are as set forth in embodiment no. 1.

5 In embodiment no. 13, the present invention provides the compound having structural Formula (I), wherein the subscript t is 0 or 1, and the remaining variables are as set forth in embodiment no. 1.

In embodiment no. 14, the present invention provides the compound having structural

Formula (I), wherein the group  is , and the remaining variables are as set forth in embodiment no. 1.

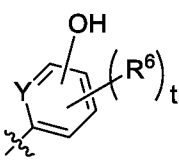
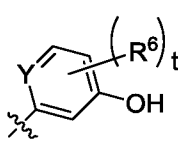
10 In embodiment no. 15, the present invention provides the compound having structural Formula (I), wherein:

R^1 is (C_1-C_6) alkyl, wherein said alkyl is unsubstituted or substituted by 1 to 6 fluoro;

Y is C(H), and the remaining variable are as set forth in embodiment no. 1.

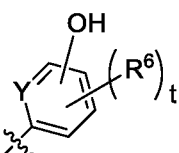
15 In embodiment no. 16, the present invention provides the compound having structural Formula (I), wherein:

R^1 is (C_1-C_6) alkyl, wherein said alkyl is unsubstituted or substituted by 1 to 6 fluoro;

the group  is ,

Y is N, and the remaining variable are as set forth in embodiment no. 1.

In embodiment no. 17, the present invention provides the compound having structural

20 Formula (I), wherein the group  is as set forth in embodiment no. 14,

X is C(H) or N;

Y is C(H) or N;

R^1 is $-CH_2-R^2$,

R^2 is unsubstituted phenyl or phenyl substituted by 1 to 3 R^{2a} ;

25 each R^{2a} is independently halo, (C_1-C_3) alkyl, or (C_1-C_3) fluoroalkyl;

R^3 is methyl;

R^{5a} and R^{5b} are H; and

the subscript t is 0 or 1.

In another embodiment, the present invention provides a compound selected from:

- 4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-
5 a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;
- 4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;
- 4-amino-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-[3-hydroxy-4-(trifluoromethyl)phenyl]-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;
- 10 4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;
- 4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;
- 15 4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;
- 4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-5-methyl-2-{8-[(2,3,5-trifluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;
- 20 4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;
- 4-amino-5-(3,4-difluoro-5-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;
- 25 4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;
- 4-amino-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;
- 30 4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;
- 4-amino-5-(4-fluoro-3-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-(4-amino-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

5 4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 4-(4-amino-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

15 4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3,4-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-{8-[(2,4-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 4-(4-amino-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

4-amino-5-(3-fluoro-4-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 4-amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-(4-amino-2-{8-[(3,5-difluorophenyl)methyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl}-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

30 4-amino-5-(3-chloro-4-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(3-fluoro-4-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-2-{8-[(2,3,5-trifluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 4-amino-2-{8-[(2,4-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(3-chloro-4-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

15 4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-fluoro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-(4-amino-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

20 4-amino-2-(8-butylimidazo[1,2-*a*]pyrazin-6-yl)-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 4-amino-5-(3-fluoro-4-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 4-amino-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-chlorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(4-hydroxy-3-methylphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-fluoro-3-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 4-amino-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(5-chloro-6-hydroxypyridin-2-yl)-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-(8-butylimidazo[1,2-*a*]pyrazin-6-yl)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

15 4-amino-5-(4-chloro-5-hydroxypyridin-2-yl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(3-fluoro-4-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 4-amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(4,4,4-trifluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-{8-[(4-chlorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 4-amino-5-(4-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(3-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 4-amino-5-(3-chloro-4-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 4-amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(3-chloro-4-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 4-amino-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(2,4-dichloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(2,4-dichloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

15 4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 4-amino-2-(8-butylimidazo[1,2-*a*]pyrazin-6-yl)-5-(5-chloro-4-hydroxypyridin-2-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(3,5-dichloro-4-hydroxypyridin-2-yl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(3-chloro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-(8-butylimidazo[1,2-*a*]pyrazin-6-yl)-5-(3-chloro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-(8-butylimidazo[1,2-*a*]pyrazin-6-yl)-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 4-amino-5-(3-chloro-4-hydroxyphenyl)-2-(8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 4-amino-5-(4-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 4-amino-2-(8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-(8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-(8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

15 4-amino-2-(8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(4,4,4-trifluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 4-amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(3-chloro-4-hydroxyphenyl)-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2,6-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2,4-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-((4,4-difluorocyclohexyl)methyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(3-chloro-4-fluoro-2-hydroxyphenyl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(3-fluoro-5-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(2,6-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]-2-methylimidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]-2-methylimidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-(4-amino-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

4-(4-amino-5-methyl-6-oxo-2-{8-[(2,3,5-trifluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-5-methyl-2-{8-[(2,3,5-trifluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-chloro-5-hydroxypyridin-2-yl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-(4-fluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxy-4-methylphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-{8-[(4-methylcyclohexyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(4-hydroxypyridin-2-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-{8-[(3-fluorophenyl)methyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl}-5-(4-hydroxypyridin-2-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 4-amino-5-(3-chloro-4-hydroxypyridin-2-yl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(3,5-dichloro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 4-amino-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(3,5-dichloro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

15 4-amino-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(4-hydroxypyridin-2-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(4-hydroxypyridin-2-yl)-2-(8-isopentyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 4-amino-5-(3-chloro-4-hydroxyphenyl)-5-methyl-2-{8-[(4-methylcyclohexyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 4-amino-5-(3-hydroxyphenyl)-5-methyl-2-{8-[(3-methylphenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-(8-benzylimidazo[1,2-*a*]pyrazin-6-yl)-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-{8-[(3-chlorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-5-(3-fluoro-4-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-{8-[(3-chlorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 4-amino-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-2-{8-[(3-methylphenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-(8-benzylimidazo[1,2-*a*]pyrazin-6-yl)-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 5-(4-fluoro-3-hydroxyphenyl)-4-(3-hydroxy-3-(trifluoromethyl)azetidin-1-yl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5-(3-fluoro-4-hydroxyphenyl)-4-(3-hydroxy-3-(trifluoromethyl)azetidin-1-yl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

15 5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-4-[(3,3,3-trifluoro-2-hydroxypropyl)amino]-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-4-[(3,3,3-trifluoro-2-hydroxypropyl)amino]-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-4-[(3,3,3-trifluoro-2-hydroxypropyl)amino]-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-4-(4-methylpiperazin-1-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-(4,4-difluoropiperidin-1-yl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 5-(4-chloro-3-hydroxyphenyl)-4-(4,4-difluoropiperidin-1-yl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-4-(4-(trifluoromethyl)piperidin-1-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-4-((3,3,3-trifluoropropyl)amino)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-4-((4,4,4-trifluorobutyl)amino)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one; and

4-amino-2-(3-amino-8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one; or
a pharmaceutically acceptable salt thereof.

10 In another embodiment, the present invention provides a compound selected from:

(5*R*)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-[3-hydroxy-4-(trifluoromethyl)phenyl]-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-5-methyl-2-{8-[(2,3,5-trifluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 (5*R*)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(3,4-difluoro-5-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 (5R)-4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-fluoro-3-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 (5R)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-(4-amino-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

(5R)-4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-(4-amino-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

(5R)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3,4-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-2-{8-[(2,4-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-(4-amino-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

(5R)-4-amino-5-(3-fluoro-4-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 (5R)-4-(4-amino-2-{8-[(3,5-difluorophenyl)methyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl}-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

(5R)-4-amino-5-(3-chloro-4-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 (5R)-4-amino-5-(3-fluoro-4-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

15 (5R)-4-amino-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-2-{8-[(2,3,5-trifluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 (5R)-4-amino-2-{8-[(2,4-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(3-chloro-4-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 (5R)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-fluoro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 (5R)-4-(4-amino-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

(5R)-4-amino-2-(8-butylimidazo[1,2-*a*]pyrazin-6-yl)-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(3-fluoro-4-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-chlorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(4-hydroxy-3-methylphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(4-fluoro-3-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(5-chloro-6-hydroxypyridin-2-yl)-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-2-(8-butylimidazo[1,2-*a*]pyrazin-6-yl)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(4-chloro-5-hydroxypyridin-2-yl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(3-fluoro-4-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(4,4,4-trifluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-2-{8-[(4-chlorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 (5*R*)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(4-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 (5*R*)-4-amino-5-(3-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(3-chloro-4-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

15 (5*R*)-4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 (5*R*)-4-amino-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-5-(3-chloro-4-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 (5*R*)-4-amino-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(2,4-dichloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 (5*R*)-4-amino-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(2,4-dichloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-2-(8-butylimidazo[1,2-*a*]pyrazin-6-yl)-5-(5-chloro-4-hydroxypyridin-2-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(3,5-dichloro-4-hydroxypyridin-2-yl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(3-chloro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-2-(8-butylimidazo[1,2-*a*]pyrazin-6-yl)-5-(3-chloro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-2-(8-butylimidazo[1,2-*a*]pyrazin-6-yl)-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(3-chloro-4-hydroxyphenyl)-2-(8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-2-(8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-2-(8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-2-(8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-2-(8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(4,4,4-trifluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(3-chloro-4-hydroxyphenyl)-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 (5R)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2,6-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2,4-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 (5R)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

15 (5R)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-((4,4-difluorocyclohexyl)methyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(3-chloro-4-fluoro-2-hydroxyphenyl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 (5R)-4-amino-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(3-fluoro-5-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(2,6-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 (5R)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]-2-methylimidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]-2-methylimidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-(4-amino-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

(5R)-4-(4-amino-5-methyl-6-oxo-2-{8-[(2,3,5-trifluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-

5 hydroxybenzonitrile;

(5R)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-5-methyl-2-{8-[(2,3,5-trifluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 (5R)-4-amino-5-(4-chloro-5-hydroxypyridin-2-yl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

15 (5R)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-(4-fluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxy-4-methylphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 (5R)-4-amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-{8-[(*trans*-4-methylcyclohexyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-{8-[(*cis*-4-methylcyclohexyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 (5R)-4-amino-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(4-hydroxypyridin-2-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-2-{8-[(3-fluorophenyl)methyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl}-5-(4-hydroxypyridin-2-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 (5R)-4-amino-5-(3-chloro-4-hydroxypyridin-2-yl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(3,5-dichloro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(3,5-dichloro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 (5R)-4-amino-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 (5R)-4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(4-hydroxypyridin-2-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(4-hydroxypyridin-2-yl)-2-(8-isopentyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

15 (5R)-4-amino-5-(3-chloro-4-hydroxyphenyl)-5-methyl-2-{8-[(*trans*-4-methylcyclohexyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(3-chloro-4-hydroxyphenyl)-5-methyl-2-{8-[(*cis*-4-methylcyclohexyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 (5R)-4-amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(3-hydroxyphenyl)-5-methyl-2-{8-[(3-methylphenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 (5R)-4-amino-2-(8-benzylimidazo[1,2-*a*]pyrazin-6-yl)-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-2-{8-[(3-chlorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(3-fluoro-4-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 (5R)-4-amino-2-{8-[(3-chlorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-2-{8-[(3-methylphenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-amino-2-(8-benzylimidazo[1,2-*a*]pyrazin-6-yl)-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-5-(4-fluoro-3-hydroxyphenyl)-4-(3-hydroxy-3-(trifluoromethyl)azetidin-1-yl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-5-(3-fluoro-4-hydroxyphenyl)-4-(3-hydroxy-3-(trifluoromethyl)azetidin-1-yl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-5-(4-Chloro-3-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-4-{[(2R)-3,3,3-trifluoro-2-hydroxypropyl]amino}-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one

(5R)-5-(4-Chloro-3-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-4-{[(2S)-3,3,3-trifluoro-2-hydroxypropyl]amino}-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one

(5R)-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-4-{[(2R)-3,3,3-trifluoro-2-hydroxypropyl]amino}-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-4-{[(2S)-3,3,3-trifluoro-2-hydroxypropyl]amino}-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-4-{[(2R)-3,3,3-trifluoro-2-hydroxypropyl]amino}-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-4-{[(2S)-3,3,3-trifluoro-2-hydroxypropyl]amino}-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-4-(4-methylpiperazin-1-yl)-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-4-(4,4-difluoropiperidin-1-yl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5R)-5-(4-chloro-3-hydroxyphenyl)-4-(4,4-difluoropiperidin-1-yl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-4-(4-(trifluoromethyl)piperidin-1-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-4-((3,3,3-trifluoropropyl)amino)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*R*)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-4-((4,4,4-trifluorobutyl)amino)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one; and

(5*R*)-4-amino-2-(3-amino-8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one; or a pharmaceutically salt thereof.

In another embodiment, the present invention provides a compound selected from:

(5*S*)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-[3-hydroxy-4-(trifluoromethyl)phenyl]-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-5-methyl-2-{8-[(2,3,5-trifluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(3,4-difluoro-5-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-fluoro-3-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-(4-amino-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

(5S)-4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-(4-amino-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

(5S)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3,4-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-{8-[(2,4-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-(4-amino-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

(5S)-4-amino-5-(3-fluoro-4-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 (5S)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 (5S)-4-(4-amino-2-{8-[(3,5-difluorophenyl)methyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl}-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

(5S)-4-amino-5-(3-chloro-4-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(3-fluoro-4-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

15 (5S)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 (5S)-4-amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-2-{8-[(2,3,5-trifluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 (5S)-4-amino-2-{8-[(2,4-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(3-chloro-4-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 (5S)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-fluoro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-(4-amino-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

(5S)-4-amino-2-(8-butylimidazo[1,2-*a*]pyrazin-6-yl)-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(3-fluoro-4-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-chlorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(4-hydroxy-3-methylphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-fluoro-3-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(5-chloro-6-hydroxypyridin-2-yl)-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-(8-butylimidazo[1,2-*a*]pyrazin-6-yl)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-chloro-5-hydroxypyridin-2-yl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-5-(3-fluoro-4-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(4,4,4-trifluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 (5*S*)-4-amino-2-{8-[(4-chlorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 (5*S*)-4-amino-5-(4-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-5-(3-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-5-(3-chloro-4-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

15 (5*S*)-4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 (5*S*)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-2-(8-isopentylimidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 (5*S*)-4-amino-5-(3-chloro-4-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(2,4-dichloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 (5*S*)-4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(2,4-dichloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-2-(8-butylimidazo[1,2-*a*]pyrazin-6-yl)-5-(5-chloro-4-hydroxypyridin-2-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 (5*S*)-4-amino-5-(3,5-dichloro-4-hydroxypyridin-2-yl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(3-chloro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 (5*S*)-4-amino-2-(8-butylimidazo[1,2-*a*]pyrazin-6-yl)-5-(3-chloro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-2-(8-butylimidazo[1,2-*a*]pyrazin-6-yl)-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

15 (5*S*)-4-amino-5-(3-chloro-4-hydroxyphenyl)-2-(8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-5-(3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-5-(3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 (5*S*)-4-amino-5-(4-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-5-(4-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 (5*S*)-4-amino-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-2-(8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-2-(8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 (5*S*)-4-amino-2-(8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-2-(8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(4,4,4-trifluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 (5S)-4-amino-5-(3-chloro-4-hydroxyphenyl)-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2,6-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 (5S)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2,4-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

15 (5S)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 (5S)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-((4,4-difluorocyclohexyl)methyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(3-chloro-4-fluoro-2-hydroxyphenyl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 (5S)-4-amino-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(3-fluoro-5-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(2,6-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 (5S)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]-2-methylimidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]-2-methylimidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-(4-amino-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

5 (5S)-4-(4-amino-5-methyl-6-oxo-2-{8-[(2,3,5-trifluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile;

(5S)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-5-methyl-2-{8-[(2,3,5-trifluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 (5S)-4-amino-5-(4-chloro-5-hydroxypyridin-2-yl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-(4-fluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxy-4-methylphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 (5S)-4-amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-{8-[(*trans*-4-methylcyclohexyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-{8-[(*cis*-4-methylcyclohexyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(4-hydroxypyridin-2-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-{8-[(3-fluorophenyl)methyl]-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl}-5-(4-hydroxypyridin-2-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 (5S)-4-amino-5-(3-chloro-4-hydroxypyridin-2-yl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(3,5-dichloro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-(8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazin-6-yl)-5-(3,5-dichloro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 (5S)-4-amino-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 (5S)-4-amino-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-(8-butyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-(4-hydroxypyridin-2-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(4-hydroxypyridin-2-yl)-2-(8-isopentyl-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

15 (5S)-4-amino-5-(3-chloro-4-hydroxyphenyl)-5-methyl-2-{8-[(*trans*-4-methylcyclohexyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(3-chloro-4-hydroxyphenyl)-5-methyl-2-{8-[(*cis*-4-methylcyclohexyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 (5S)-4-amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(3-hydroxyphenyl)-5-methyl-2-{8-[(3-methylphenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 (5S)-4-amino-2-(8-benzylimidazo[1,2-*a*]pyrazin-6-yl)-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-{8-[(3-chlorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 (5S)-4-amino-5-(3-fluoro-4-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-2-{8-[(3-chlorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-amino-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-2-{8-[(3-methylphenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 (5S)-4-amino-2-(8-benzylimidazo[1,2-*a*]pyrazin-6-yl)-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-5-(4-fluoro-3-hydroxyphenyl)-4-(3-hydroxy-3-(trifluoromethyl)azetidin-1-yl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 (5S)-5-(3-fluoro-4-hydroxyphenyl)-4-(3-hydroxy-3-(trifluoromethyl)azetidin-1-yl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]amino}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

15 (5S)-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-4-[(2*R*)-3,3,3-trifluoro-2-hydroxypropyl]amino}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 (5S)-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]amino}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-4-[(2*R*)-3,3,3-trifluoro-2-hydroxypropyl]amino}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 (5S)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-4-[(2*S*)-3,3,3-trifluoro-2-hydroxypropyl]amino}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-4-[(2*R*)-3,3,3-trifluoro-2-hydroxypropyl]amino}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 (5S)-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-4-(4-methylpiperazin-1-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5S)-4-(4,4-difluoropiperidin-1-yl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-5-(4-chloro-3-hydroxyphenyl)-4-(4,4-difluoropiperidin-1-yl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-4-(4-(trifluoromethyl)piperidin-1-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-4-((3,3,3-trifluoropropyl)amino)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-4-((4,4,4-trifluorobutyl)amino)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(5*S*)-4-amino-2-(3-amino-8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

or a pharmaceutically acceptable salt thereof.

The present invention includes the pharmaceutically acceptable salts of the compounds defined herein, including the pharmaceutically acceptable salts of all structural formulas, embodiments and classes defined herein.

"Alkyl", as well as other groups having the prefix "alk", such as alkoxy, and the like, means carbon chains which may be linear or branched, or combinations thereof, containing the indicated number of carbon atoms. If no number is specified, 1-6 carbon atoms are intended for linear and 3-7 carbon atoms for branched alkyl groups. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and *tert*-butyl, pentyl, hexyl, heptyl, octyl, nonyl and the like.

"Alkoxy" and "alkyl-O-" are used interchangeably and refer to an alkyl group linked to oxygen.

"Alkyl-NH-" refers to an alkyl group linked to an NH group. Examples of alkyl-NH- include methyl-amino or methyl-NH- and ethyl-amino or ethyl-NH-.

"Aryl" means phenyl or naphthyl.

"Haloalkyl" include mono- substituted as well as multiple halo substituted alkyl groups, up to perhalo substituted alkyl. For example, halomethyl, 1,1-difluoroethyl, trifluoromethyl or 1,1,1,2,2-pentafluorobutyl are included.

"Haloalkoxy" and "haloalkyl-O" are used interchangeably and refer to halo substituted alkyl groups or "haloalkyl" linked through the oxygen atom. Haloalkoxy include

mono- substituted as well as multiple halo substituted alkoxy groups, up to perhalo substituted alkoxy. For example, trifluoromethoxy is included.

"Cycloalkyl" means a saturated cyclic hydrocarbon radical having the number of carbon atoms designated if no number of atoms is specified, 3-12 carbon atoms are intended, forming 1-3 carbocyclic rings that are fused. "Cycloalkyl" also includes monocyclic rings fused to an aryl group in which the point of attachment is on the non-aromatic portion. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronaphthyl, adamantyl, decahydronaphthyl, indanyl and the like.

"Cycloalkoxy" and "cycloalkyl-O" are used interchangeably and refer to a cycloalkyl group, as defined above, linked to oxygen.

"Heterocyclyl" "heterocycle" or "heterocyclic" refers to nonaromatic monocyclic ring structures in which one or more atoms in the ring, the heteroatom(s), is an element other than carbon. Such nonaromatic cyclic ring structures can be saturated or unsaturated. Heteroatoms are typically O, S or N atoms. Examples of heterocyclyl groups include: piperidine, piperazinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, azetidiny, oxiranyl, or aziridinyl, and the like.

"Heteroaryl" refers to an aromatic monocyclic ring structures in which one or more atoms in the ring, the heteroatom(s), is an element other than carbon. Heteroatoms are typically O, S, or N atoms. Examples of heteroaromatic groups include: pyridinyl, pyrimidinyl, pyrrolyl, pyridazinyl, isoxazolyl, indolyl, or imidazolyl.

"Halogen" (or "halo") unless otherwise indicated, includes fluorine (fluoro), chlorine (chloro), bromine (bromo) and iodine (iodo). In one embodiment, halo is fluoro (-F) or chloro (-Cl).

When any variable (*e.g.*, R^{2a}, R⁶) occurs more than one time in any constituent or in Formula (I) or other generic formulas herein, its definition on each occurrence is independent of its definition at every other occurrence. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. In choosing compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, *i.e.*, R^{2a}, R⁶, etc., are to be chosen in conformity with well-known principles of chemical structure connectivity and stability. Unless expressly stated to the contrary, substitution by a named substituent is permitted on any atom in a ring (*e.g.*, aryl, a heteroaryl ring, or a saturated heterocyclic ring) provided such ring substitution is chemically allowed and results in a stable compound. A "stable" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially

unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (*e.g.*, therapeutic or prophylactic administration to a subject).

The term "substituted" shall be deemed to include multiple degrees of substitution by a named substituent. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally. By independently substituted, it is meant that the (two or more) substituents can be the same or different.

Unless expressly depicted or described otherwise, variables depicted in a structural formula with a "floating" bond, such as R⁶ in Formula (I), are permitted on any available carbon atom in the ring to which the variable is attached. When a moiety is noted as being "optionally substituted" in Formula (I) or any embodiment thereof, it means that Formula (I) or the embodiment thereof encompasses compounds that contain the noted substituent (or substituents) on the moiety and also compounds that do not contain the noted substituent (or substituents) on the moiety.

Compounds of Formula (I) may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereoisomeric mixtures and individual diastereoisomers. Centers of asymmetry that are present in the compounds of Formula (I) can all independently of one another have S configuration or R configuration. The compounds of this invention include all possible enantiomers and diastereomers and mixtures of two or more stereoisomers, for example mixtures of enantiomers and/or diastereomers, in all ratios. Thus, enantiomers are a subject of the invention in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. In the case of a cis/trans isomerism the invention includes both the cis form and the trans form as well as mixtures of these forms in all ratios. The present invention is meant to comprehend all such stereoisomeric forms of the compounds of Formula (I). Where a structural formula or chemical name specifies a particular configuration at a stereocenter, the enantiomer or stereoisomer of the compound resulting from that specified stereocenter is intended.

Compounds of Formula (I) may be separated into their individual diastereoisomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof, or via chiral chromatography using an optically active stationary phase. Absolute stereochemistry may be determined by X-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration. Alternatively, any

stereoisomer or isomers of a compound of Formula (I) may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known absolute configuration.

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

For compounds of Formula (I) described herein which contain olefinic double bonds, unless specified otherwise, they are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist as tautomers which have different points of attachment of hydrogen accompanied by one or more double bond shifts. For example, a ketone and its enol form are keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed by the compounds of Formula I of the present invention.

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

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present

invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts prepared from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines derived from both naturally occurring and synthetic sources. Pharmaceutically acceptable organic non-toxic bases from which salts can be formed include, for example, arginine, betaine, caffeine, choline, N,N'-dibenzyl-ethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, dicyclohexylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids. If the compounds of Formula (I) simultaneously contain acidic and basic groups in the molecule the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). Salts can be obtained from the compounds of Formula (I) by customary methods which are known to the person skilled in the art, for example, by combination with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange from other salts. The present invention also includes all salts of the compounds of Formula (I) which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

Furthermore, compounds of the present invention may exist in amorphous form and/or one or more crystalline forms, and as such all amorphous and crystalline forms and mixtures thereof of the compounds of Formula (I), including the Examples, are intended to be included within the scope of the present invention. In addition, some of the compounds of the

instant invention may form solvates with water (*i.e.*, a hydrate) or common organic solvents such as but not limited to ethyl acetate. Such solvates and hydrates, particularly the pharmaceutically acceptable solvates and hydrates, of the instant compounds are likewise encompassed within the scope of this invention, along with un-solvated and anhydrous forms.

Any pharmaceutically acceptable pro-drug modification of a compound of this invention which results in conversion *in vivo* to a compound within the scope of this invention is also within the scope of this invention. For example, esters can optionally be made by esterification of an available carboxylic acid (-COOH) group or by formation of an ester on an available hydroxy group in a compound. Similarly, labile amides can be made.

Pharmaceutically acceptable esters or amides of the compounds of this invention may be prepared to act as pro-drugs which can be hydrolyzed back to an acid (or -COO- depending on the pH of the fluid or tissue where conversion takes place) or hydroxy form particularly *in vivo* and as such are encompassed within the scope of this invention. Included are those esters and acyl groups known in the art for modifying the solubility or hydrolysis characteristics for use as sustained-release or prodrug formulations. Also, in the case of a carboxylic acid (-COOH) or alcohol group being present in the compounds of the present invention, pharmaceutically acceptable esters of carboxylic acid derivatives, such as methyl, ethyl, or pivaloyloxymethyl, or acyl derivatives of alcohols, such as *O*-acetyl, *O*-pivaloyl, *O*-benzoyl, and *O*-aminoacyl, can be employed.

The present invention also relates to processes for the preparation of the compounds of Formula (I) which are described in the following and by which the compounds of the invention are obtainable.

The compounds of Formula (I) according to the invention effect an increase of cGMP concentration via the activation of the soluble guanylate cyclase (sGC), and they therefore may be useful agents for the therapy and prophylaxis of disorders which are associated with a low or decreased cGMP level or which are caused thereby, or for whose therapy or prophylaxis an increase of the present cGMP level is desired. The activation of the sGC by the compounds of Formula (I) can be examined, for example, in the cell-based sGC functional assay described in the Biological Assays below.

The compounds of Formula (I) bind with high potency to sGC to enable administration of, for example, doses of less than 10 μ g. High potency compounds are preferred to enable administration of low human doses. For inhaled delivery applications, high potency compounds may enable use of low human doses, and allow for formulation within the restraints of an inhaled delivery device.

The binding potencies of the compounds of Formula (I) can be determined in a competitive binding assay that uses a labeled sGC ligand. The Biological Assays section below describes an example of a competitive binding assay used to determine the compounds' abilities to displace a radioligand that binds to purified recombinant sGC.

5 The terms "therapeutically effective (or efficacious) amount" and similar descriptions such as "an amount efficacious for treatment" are intended to mean that amount of a pharmaceutical drug that will elicit the biological or medical response of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. The terms "prophylactically effective (or efficacious) amount" and similar
10 descriptions such as "an amount efficacious for prevention" are intended to mean that amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician. As an example, the dosage a patient receives can be selected so as to achieve the desired reduction in blood pressure. The
15 dosage a patient receives may also be titrated over time in order to reach a target blood pressure. The dosage regimen utilizing a compound of the instant invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the potency of the compound chosen to be administered; the route of administration; and the renal and hepatic
20 function of the patient. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective or prophylactically effective dosage amount needed to prevent, counter, or arrest the progress of the condition. It is understood that a specific daily dosage amount can simultaneously be both a therapeutically effective amount, *e.g.*, for treatment of hypertension, and a prophylactically
25 effective amount, *e.g.*, for prevention of myocardial infarction.

Disorders and pathological conditions which are associated with a low cGMP level or in which an increase of the cGMP level is desired and for whose therapy and prophylaxis it is possible to use compounds of Formula (I) are, for example, cardiovascular diseases, such as endothelial dysfunction, diastolic dysfunction, atherosclerosis, hypertension, heart failure,
30 pulmonary hypertension (WHO Groups I, II, III, IV), which includes pulmonary arterial hypertension (PAH), stable and unstable angina pectoris, thromboses, restenoses, myocardial infarction, stroke, cardiac insufficiency, fibrosis or pulmonary hypertonia, or, for example, erectile dysfunction, asthma (*e.g.*, bronchial asthma), cirrhosis of the liver, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), acute

lung injury, pulmonary fibrosis, chronic kidney disease, chronic kidney insufficiency, cystic fibrosis, interstitial lung disease, sickle cell anemia, scleroderma, Raynaud's Syndrome, or diabetes.

In one embodiment of the invention, the compounds of Formula (I) may be used for
5 treating cardiovascular disease, endothelial dysfunction, diastolic dysfunction, atherosclerosis, hypertension, heart failure, pulmonary hypertension (WHO groups I, II, III, IV), angina pectoris, thrombosis, restenosis, myocardial infarction, stroke, cardiac insufficiency, fibrosis, pulmonary hypertonia, erectile dysfunction, asthma, chronic kidney disease, diabetes, cirrhosis of the liver, chronic obstructive pulmonary disease (COPD), acute respiratory
10 distress syndrome, acute lung injury, pulmonary fibrosis, cystic fibrosis, or interstitial lung disease.

The compounds of Formula (I) and their pharmaceutically acceptable salts can be administered to animals, preferably to mammals, and in particular to humans, as pharmaceuticals by themselves, in mixtures with one another or in the form of
15 pharmaceutical compositions. The term "patient" includes animals, preferably mammals and especially humans, who use the instant active agents for the prevention or treatment of a medical condition. Administering of the drug to the patient includes both self-administration and administration to the patient by another person. The patient may be in need of, or desire, treatment for an existing disease or medical condition, or may be in need of or desire
20 prophylactic treatment to prevent or reduce the risk of occurrence of said disease or medical condition. As used herein, a patient "in need" of treatment of an existing condition or of prophylactic treatment encompasses both a determination of need by a medical professional as well as the desire of a patient for such treatment.

Subjects of the present invention therefore also are the compounds of Formula (I) and
25 their pharmaceutically acceptable salts for use as pharmaceuticals, their use for activating soluble guanylate cyclase, for normalizing a disturbed cGMP balance and in particular their use in the therapy and prophylaxis of the above mentioned syndromes as well as their use for preparing medicaments for these purposes.

Furthermore, a subject of the present invention is pharmaceutical compositions which
30 comprise as active component an effective dose of at least one compound of Formula (I) and/or a pharmaceutically acceptable salt thereof and a customary pharmaceutically acceptable carrier, *i.e.*, one or more pharmaceutically acceptable carrier substances and/or additives.

Thus, a subject of the invention is, for example, said compound and its pharmaceutically acceptable salts for use as a pharmaceutical, pharmaceutical compositions which comprise as active component an effective dose of the compound of Formula (I) and/or a pharmaceutically acceptable salt thereof and a customary pharmaceutically acceptable carrier, and the uses of said compound and/or a pharmaceutically acceptable salt thereof in the therapy or prophylaxis of the abovementioned syndromes as well as their use for preparing medicaments for these purposes.

The pharmaceutical compositions according to the invention can be administered orally, for example in the form of pills, tablets, lacquered tablets, sugar-coated tablets, granules, hard and soft gelatin capsules, aqueous, alcoholic or oily solutions, syrups, emulsions or suspensions, or rectally, for example in the form of suppositories. Administration can also be carried out parenterally, for example subcutaneously, intramuscularly or intravenously in the form of solutions for injection or infusion.

The pharmaceutical compositions can also be administered by the inhaled route. Dosage forms for inhaled administration may conveniently be formulated as aerosols or dry powders. For compositions suitable and/or adapted for inhaled administration, it is preferred that the compound of Formula (I) is in a particle-size-reduced form, and more preferably the size-reduced form is obtained or obtainable by micronisation.

Aerosol formulations, *e.g.*, for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol formulations can be presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device or inhaler. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose inhaler) which is intended for disposal once the contents of the container have been exhausted.

Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide or an organic propellant such as a hydrofluorocarbon (HFC). Suitable HFC propellants include 1,1,1,2,3,3,3-heptafluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser. The pressurised aerosol may contain a solution or a suspension of the active compound. This may require the incorporation of additional excipients *e.g.*, co-solvents and/or surfactants to improve the dispersion characteristics and homogeneity of suspension formulations. Solution formulations may also require the addition

of co-solvents such as ethanol. Other excipient modifiers may also be incorporated to improve, for example, the stability and/or taste and/or fine particle mass characteristics (amount and/or profile) of the formulation.

Pharmaceutical compositions suitable for inhaled administration may also take the form of a dry powder inhalable composition. Such a composition can comprise a powder base such as lactose, glucose, trehalose, mannitol or starch, the compound of Formula (I) (preferably in particle-size-reduced form, *e.g.*, in micronised form), and optionally a performance modifier such as L-leucine or another amino acid, and/or metals salts of stearic acid such as magnesium or calcium stearate. In some embodiments, the dry powder inhalable composition comprises a dry powder blend of lactose and the compound of Formula (I) or salt thereof.

Optionally, in particular for dry powder inhalable compositions, a pharmaceutical composition for inhaled administration can be incorporated into a plurality of sealed dose containers (*e.g.*, containing the dry powder composition) mounted longitudinally in a strip or ribbon inside a suitable inhalation device. The container is rupturable or peel-openable on demand and the dose of *e.g.*, the dry powder composition can be administered by inhalation via the device such as the DISKUS® device (GlaxoSmithKline). Other dry powder inhalers are well known to those of ordinary skill in the art, and many such devices are commercially available, with representative devices including Aerolizer® (Novartis), Airmax™ (IVAX), ClickHaler® (Innovata Biomed), Diskhaler® (GlaxoSmithKline), Accuhaler (GlaxoSmithKline), Easyhaler® (Orion Pharma), Eclipse™ (Aventis), FlowCaps® (Hovione), Handihaler® (Boehringer Ingelheim), Pulvinal® (Chiesi), Rotahaler® (GlaxoSmithKline), SkyeHaler™ or Certihaler™ (SkyePharma), Twisthaler (Merck & Co., Inc.), Turbuhaler® (AstraZeneca), Ultrahaler® (Aventis), and the like.

Other suitable administration forms are, for example, percutaneous or topical administration, for example in the form of ointments, tinctures, sprays or transdermal therapeutic systems, or, for example, microcapsules, implants or rods. The preferred administration form depends, for example, on the disease to be treated and on its severity.

The amount of active compound of Formula (I) and/or its pharmaceutically acceptable salts in the pharmaceutical composition normally is from 0.1 to 200 mg, preferably from 1 to 200 mg, per dose, but depending on the type of the pharmaceutical composition it can also be higher. The pharmaceutical compositions usually comprise 0.5 to 90 percent by weight of the compound of Formula (I) and/or their pharmaceutically acceptable salts. The preparation of the pharmaceutical compositions can be carried out in a manner known *per se*. For this

purpose, one or more compounds of Formula (I) and/or their pharmaceutically acceptable salts, together with one or more solid or liquid pharmaceutical carrier substances and/or additives (or auxiliary substances) and, if desired, in combination with other pharmaceutically active compounds having therapeutic or prophylactic action, are brought
5 into a suitable administration form or dosage form which can then be used as a pharmaceutical in human or veterinary medicine.

For the production of pills, tablets, sugar-coated tablets and hard gelatin capsules, it is possible to use, for example, lactose, starch, for example maize starch, or starch derivatives, talc, stearic acid or its salts, etc. Carriers for soft gelatin capsules and suppositories are, for
10 example, fats, waxes, semisolid and liquid polyols, natural or hardened oils, etc. Suitable carriers for the preparation of solutions, for example of solutions for injection, or of emulsions or syrups are, for example, water, physiologically acceptable sodium chloride solution, alcohols such as ethanol, glycerol, polyols, sucrose, invert sugar, glucose, mannitol, vegetable oils, etc. It is also possible to lyophilize the compounds of Formula (I) and their
15 pharmaceutically acceptable salts and to use the resulting lyophilisates, for example, for preparing preparations for injection or infusion. Suitable carriers for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid.

Besides the active compounds and carriers, the pharmaceutical compositions can also contain customary additives, for example fillers, disintegrants, binders, lubricants, wetting
20 agents, stabilizers, emulsifiers, dispersants, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants.

The dosage of the active compound of Formula (I) and/or of a pharmaceutically acceptable salt thereof to be administered depends on the individual case and is, as is
25 customary, to be adapted to the individual circumstances to achieve an optimum effect. Thus, it depends on the nature and the severity of the disorder to be treated, and also on the sex, age, weight and individual responsiveness of the human or animal to be treated, on the efficacy and duration of action of the compounds used, on whether the therapy is acute or chronic or prophylactic, on the selected route of administration, or on whether other active compounds
30 are administered in addition to compounds of Formula (I). In general, a daily dose of approximately 0.001 to 100 mg/kg, such as 0.001 to 0.150 mg/kg, 0.01 to 10 mg/kg, or 0.3 to 5 mg/kg (in each case mg per kg of bodyweight) is appropriate for administration to an adult weighing approximately 75 kg in order to obtain the desired results. The daily dose can be administered in a single dose or, in particular when larger amounts are administered, be

divided into several, for example two, three or four individual doses. In some cases, depending on the individual response, it may be necessary to deviate upwards or downwards from the given daily dose. A single daily dose is preferred.

5 The compounds of Formula (I) activate soluble guanylate cyclase. Due to this property, apart from use as pharmaceutically active compounds in human medicine and veterinary medicine, they can also be employed as a scientific tool or as an aid for biochemical investigations in which such an effect on soluble guanylate cyclase is intended, and also for diagnostic purposes, for example in the *in vitro* diagnosis of cell samples or tissue samples. The compounds of Formula (I) and salts thereof can furthermore be employed,
10 as already mentioned above, as intermediates for the preparation of other pharmaceutically active compounds.

One or more additional pharmacologically active agents may be administered in combination with a compound of Formula (I). An additional active agent (or agents) is intended to mean a pharmaceutically active agent (or agents) that is active in the body,
15 including pro-drugs that convert to pharmaceutically active form after administration, which are different from the compound of Formula (I), and also includes free-acid, free-base and pharmaceutically acceptable salts of said additional active agents. Generally, any suitable additional active agent or agents, including but not limited to anti-hypertensive agents, anti-atherosclerotic agents such as a lipid modifying compound, anti-diabetic agents and/or anti-
20 obesity agents may be used in any combination with the compound of Formula (I) in a single dosage formulation (a fixed dose drug combination), or may be administered to the patient in one or more separate dosage formulations which allows for concurrent or sequential administration of the active agents (co-administration of the separate active agents). Examples of additional active agents which may be employed include but are not limited to
25 angiotensin converting enzyme inhibitors (e.g., alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, moveltipril, perindopril, quinapril, ramipril, spirapril, temocapril, or trandolapril), angiotensin II receptor antagonists (e.g., losartan *i.e.*, COZAAR®, valsartan, candesartan, olmesartan, telmesartan and any of these drugs used in combination with hydrochlorothiazide such as HYZAAR®);
30 neutral endopeptidase inhibitors (e.g., thiorphan and phosphoramidon), aldosterone antagonists, aldosterone synthase inhibitors, renin inhibitors (e.g. urea derivatives of di- and tri-peptides (See U.S. Pat. No. 5,116,835), amino acids and derivatives (U.S. Patents 5,095,119 and 5,104,869), amino acid chains linked by non-peptidic bonds (U.S. Patent 5,114,937), di- and tri-peptide derivatives (U.S. Patent 5,106,835), peptidyl amino diols (U.S.

Patents 5,063,208 and 4,845,079) and peptidyl beta-aminoacyl aminodiol carbamates (U.S. Patent 5,089,471); also, a variety of other peptide analogs as disclosed in the following U.S. Patents 5,071,837; 5,064,965; 5,063,207; 5,036,054; 5,036,053; 5,034,512 and 4,894,437, and small molecule renin inhibitors (including diol sulfonamides and sulfinyls (U.S. Patent 5,098,924), N-morpholino derivatives (U.S. Patent 5,055,466), N-heterocyclic alcohols (U.S. Patent 4,885,292) and pyroimidazolones (U.S. Patent 5,075,451); also, pepstatin derivatives (U.S. Patent 4,980,283) and fluoro- and chloro-derivatives of statone-containing peptides (U.S. Patent 5,066,643), enalkrein, RO 42-5892, A 65317, CP 80794, ES 1005, ES 8891, SQ 34017, aliskiren (2(S),4(S),5(S),7(S)-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)-phenyl]-octanamid hemifumarate) SPP600, SPP630 and SPP635), endothelin receptor antagonists, phosphodiesterase-5 inhibitors (*e.g.*, sildenafil, tadalafil and vardenafil), vasodilators, calcium channel blockers (*e.g.*, amlodipine, nifedipine, verapamil, diltiazem, gallopamil, niludipine, nimodipins, nicardipine), potassium channel activators (*e.g.*, nicorandil, pinacidil, cromakalim, minoxidil, aprilkalim, loprazolam), diuretics (*e.g.*, hydrochlorothiazide), sympatholitics, beta-adrenergic blocking drugs (*e.g.*, propranolol, atenolol, bisoprolol, carvedilol, metoprolol, or metoprolol tartate), alpha adrenergic blocking drugs (*e.g.*, doxazosin, prazosin or alpha methyl dopa) central alpha adrenergic agonists, peripheral vasodilators (*e.g.*, hydralazine); lipid lowering agents *e.g.*, HMG-CoA reductase inhibitors such as simvastatin and lovastatin which are marketed as ZOCOR® and MEVACOR® in lactone pro-drug form and function as inhibitors after administration, and pharmaceutically acceptable salts of dihydroxy open ring acid HMG-CoA reductase inhibitors such as atorvastatin (particularly the calcium salt sold in LIPITOR®), rosuvastatin (particularly the calcium salt sold in CRESTOR®), pravastatin (particularly the sodium salt sold in PRAVACHOL®), and fluvastatin (particularly the sodium salt sold in LESCOL®); a cholesterol absorption inhibitor such as ezetimibe (ZETIA®) and ezetimibe in combination with any other lipid lowering agents such as the HMG-CoA reductase inhibitors noted above and particularly with simvastatin (VYTORIN®) or with atorvastatin calcium; niacin in immediate-release or controlled release forms, and/or with an HMG-CoA reductase inhibitor; niacin receptor agonists such as acipimox and acifran, as well as niacin receptor partial agonists; metabolic altering agents including insulin and insulin mimetics (*e.g.*, insulin degludec, insulin glargine, insulin lispro), dipeptidyl peptidase-IV (DPP-4) inhibitors (*e.g.*, sitagliptin, alogliptin, omarigliptin, linagliptin, vildagliptin); insulin sensitizers, including (i) PPAR γ agonists, such as the glitazones (*e.g.* pioglitazone, AMG 131, MBX2044, mitoglitazone, lobeglitazone, IDR-105, rosiglitazone, and

balaglitazone), and other PPAR ligands, including (1) PPAR α/γ dual agonists (*e.g.*, ZYH2, ZYH1, GFT505, chiglitazar, muraglitazar, aleglitazar, sodelglitazar, and naveglitazar); (2) PPAR α agonists such as fenofibric acid derivatives (*e.g.*, gemfibrozil, clofibrate, ciprofibrate, fenofibrate, bezafibrate), (3) selective PPAR γ modulators (SPPAR γ M's), (*e.g.*, such as those disclosed in WO 02/060388, WO 02/08188, WO 2004/019869, WO 2004/020409, WO 2004/020408, and WO 2004/066963); and (4) PPAR γ partial agonists; (ii) biguanides, such as metformin and its pharmaceutically acceptable salts, in particular, metformin hydrochloride, and extended-release formulations thereof, such as GlumetzaTM, FortametTM, and GlucophageXRTM; and (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors (*e.g.*, ISIS-113715 and TTP814); insulin or insulin analogs (*e.g.*, insulin detemir, insulin glulisine, insulin degludec, insulin glargine, insulin lispro and inhalable formulations of each); leptin and leptin derivatives and agonists; amylin and amylin analogs (*e.g.*, pramlintide); sulfonylurea and non-sulfonylurea insulin secretagogues (*e.g.*, tolbutamide, glyburide, glipizide, glimepiride, mitiglinide, meglitinides, nateglinide and repaglinide); α -glucosidase inhibitors (*e.g.*, acarbose, voglibose and miglitol); glucagon receptor antagonists (*e.g.*, MK-3577, MK-0893, LY-2409021 and KT6-971); incretin mimetics, such as GLP-1, GLP-1 analogs, derivatives, and mimetics; and GLP-1 receptor agonists (*e.g.*, dulaglutide, semaglutide, albiglutide, exenatide, liraglutide, lixisenatide, taspoglutide, CJC-1131, and BIM-51077, including intranasal, transdermal, and once-weekly formulations thereof); LDL cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (*e.g.*, simvastatin, lovastatin, pravastatin, cerivastatin, fluvastatin, atorvastatin, and rosuvastatin), (ii) bile acid sequestering agents (*e.g.*, colestilan, colestimide, colesevalam hydrochloride, colestipol, cholestyramine, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) inhibitors of cholesterol absorption, (*e.g.*, ezetimibe), and (iv) acyl CoA:cholesterol acyltransferase inhibitors, (*e.g.*, avasimibe); HDL-raising drugs, (*e.g.*, niacin and nicotinic acid receptor agonists, and extended-release versions thereof); antiobesity compounds; agents intended for use in inflammatory conditions, such as aspirin, non-steroidal anti-inflammatory drugs or NSAIDs, glucocorticoids, and selective cyclooxygenase-2 or COX-2 inhibitors; glucokinase activators (GKAs) (*e.g.*, AZD6370); inhibitors of 11 β -hydroxysteroid dehydrogenase type 1, (*e.g.*, such as those disclosed in U.S. Patent No. 6,730,690, and LY-2523199); CETP inhibitors (*e.g.*, anacetrapib); inhibitors of fructose 1,6-bisphosphatase, (*e.g.*, such as those disclosed in U.S. Patent Nos. 6,054,587; 6,110,903; 6,284,748; 6,399,782; and 6,489,476); inhibitors of acetyl CoA carboxylase-1 or 2 (ACC1 or ACC2); AMP-activated Protein Kinase (AMPK) activators; other agonists of the G-protein-coupled receptors: (i) GPR-109, (ii)

GPR-119 (*e.g.*, MBX2982 and PSN821), and (iii) GPR-40; SSTR3 antagonists (*e.g.*, such as those disclosed in WO 2009/001836); neuromedin U receptor agonists (*e.g.*, such as those disclosed in WO 2009/042053, including, but not limited to, neuromedin S (NMS)); SCD modulators; GPR-105 antagonists (*e.g.*, such as those disclosed in WO 2009/000087); SGLT inhibitors (*e.g.*, ASP1941, SGLT-3, empagliflozin, dapagliflozin, ertugliflozin, canagliflozin, BI-10773, PF-04971729, remogloflozin, TS-071, tofogliflozin, ipragliflozin, and LX-4211); inhibitors of acyl coenzyme A:diacylglycerol acyltransferase 1 and 2 (DGAT-1 and DGAT-2); inhibitors of fatty acid synthase; inhibitors of acyl coenzyme A:monoacylglycerol acyltransferase 1 and 2 (MGAT-1 and MGAT-2); agonists of the TGR5 receptor (also known as GPBAR1, BG37, GPCR19, GPR131, and M-BAR); ileal bile acid transporter inhibitors; PACAP, PACAP mimetics, and PACAP receptor 3 agonists; PPAR agonists; protein tyrosine phosphatase-1B (PTP-1B) inhibitors; IL-1b antibodies, (*e.g.*, XOMA052 and canakinumab); and bromocriptine mesylate and rapid-release formulations thereof; or with other drugs beneficial for the prevention or the treatment of the above-mentioned diseases including nitroprusside and diazoxide the free-acid, free-base; bronchodilators such as β_2 agonist agents (*e.g.*, albuterol, terbutaline, salmeterol, and formoterol) and anticholinergic agents (*e.g.*, ipratropium bromide and tiotropium bromide); corticosteroids (*e.g.*, beclomethasone, methylprednisolone, betamethasone, prednisone, triamcinolone, dexamethasone, fluticasone, flunisolide, hydrocortisone, and corticosteroid analogs (*e.g.*, budesonide)); and pharmaceutically acceptable salt forms of the above active agents where chemically possible.

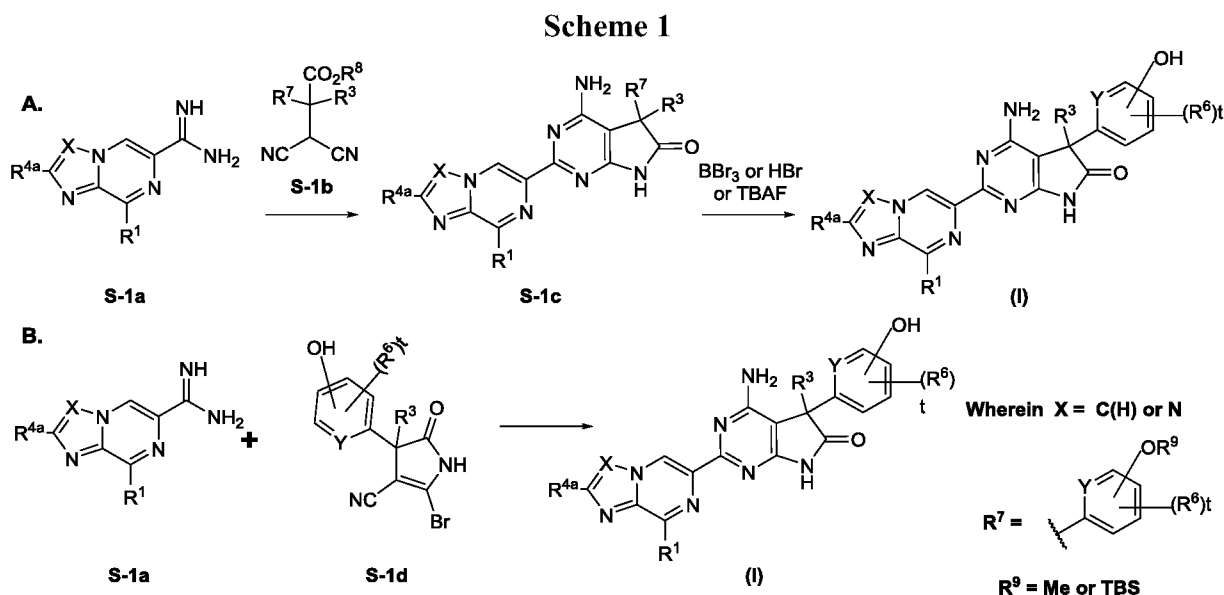
In a particular embodiment, the additional active therapeutic agent which may be administered in combination with the compound of Formula (I) is selected from an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a neutral endopeptidase inhibitor, an aldosterone antagonist, a renin inhibitor, an endothelin receptor antagonist, an aldosterone synthase inhibitor, a phosphodiesterase-5 inhibitor, a vasodilator, a calcium channel blocker, a potassium channel activator, a diuretic, a sympatholytic, a beta-adrenergic blocking drug, an alpha adrenergic blocking drug, a central alpha adrenergic agonist, a peripheral vasodilator, a lipid lowering agent, metabolic altering agent, a β_2 agonist, an anticholinergic, a corticosteroid or a corticosteroid analog.

The following examples are provided so that the invention might be more fully understood. Unless otherwise indicated, the starting materials are commercially available. They should not be construed as limiting the invention in any way.

Several methods for preparing the compounds of this invention are described in the following Schemes and Examples. Starting materials and intermediates are purchased, made

from known procedures, or as otherwise illustrated. Some frequently applied routes to the compounds of Formula (I) are also described by the Schemes as follows. In some cases the order of carrying out the steps of reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The "R," "X," and "Y" groups in the Schemes correspond to the variables defined in Formula (I) at the same positions on the structures.

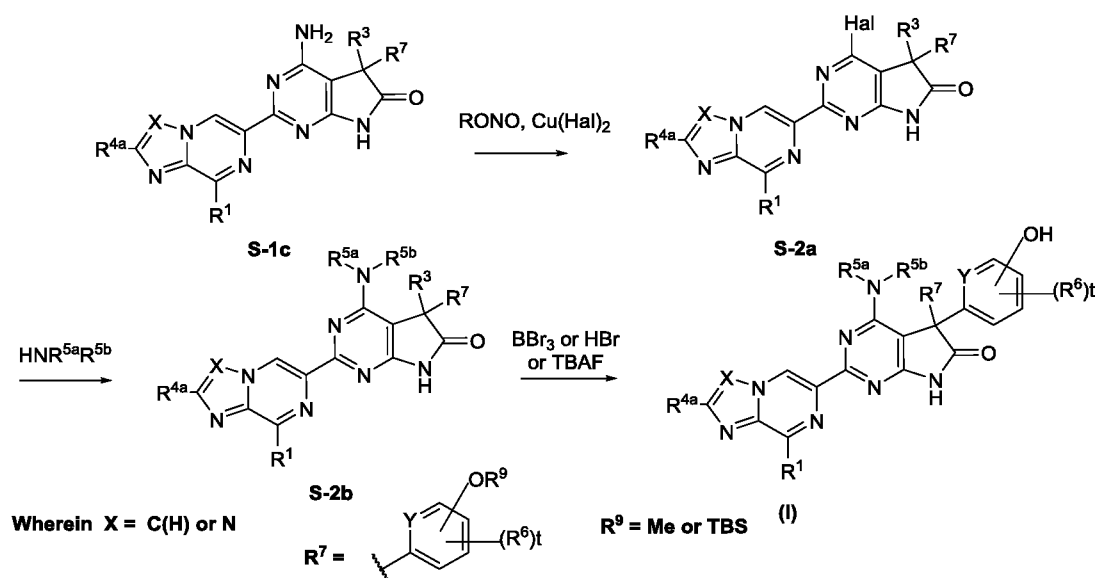
Scheme 1, in lines A and B, illustrates the general approach to assembling compounds of structural Formula (I) when X is C(H) or N and R^{5a}, R^{5b} are both H. Thus, coupling of the amidine **S-1a** to the malononitrile **S-1b** in an alcoholic solvent, such as *t*-BuOH, in the presence of a suitable inorganic base such as NaHCO₃, KHCO₃, or Na₂CO₃ at an elevated temperature, provides compound **S-1c**. Upon a treatment with an appropriate deprotecting reagent such as BBr₃, HBr or TBAF in a solvent such as DCM or THF, **S-1c** can be converted into compound of Formula (I). Alternatively, compounds of structural Formula (I) can be assembled via coupling of the amidine **S-1a** to the lactam intermediate **S-1d** in the presence of an amine base such as Et₃N in a suitable solvent such as dioxane or THF at elevated temperature.



Compounds with N-alkyl substitution at R⁵ position (when R^{5a} and/or R^{5b} are not H) can be prepared as outlined in **Scheme 2**. Treatment of the intermediate **S-1c** with a suitable diazotizing reagent such as *tert*-butyl nitrite or isopentyl nitrite in a non-polar solvent such as 1,2-DCE or DMF in a presence of excess copper(II) chloride or copper(II) bromide can provide the respective halogenated intermediate **S-2a**. Treatment of **S-2a** with an excess of amine HN(R^{5a})(R^{5b}) in a suitable solvent, such as 1,2-DCE, DMF, DMA, MeOH or THF, with or without a base additive at elevated temperatures may result in the conversion of **S-2a**

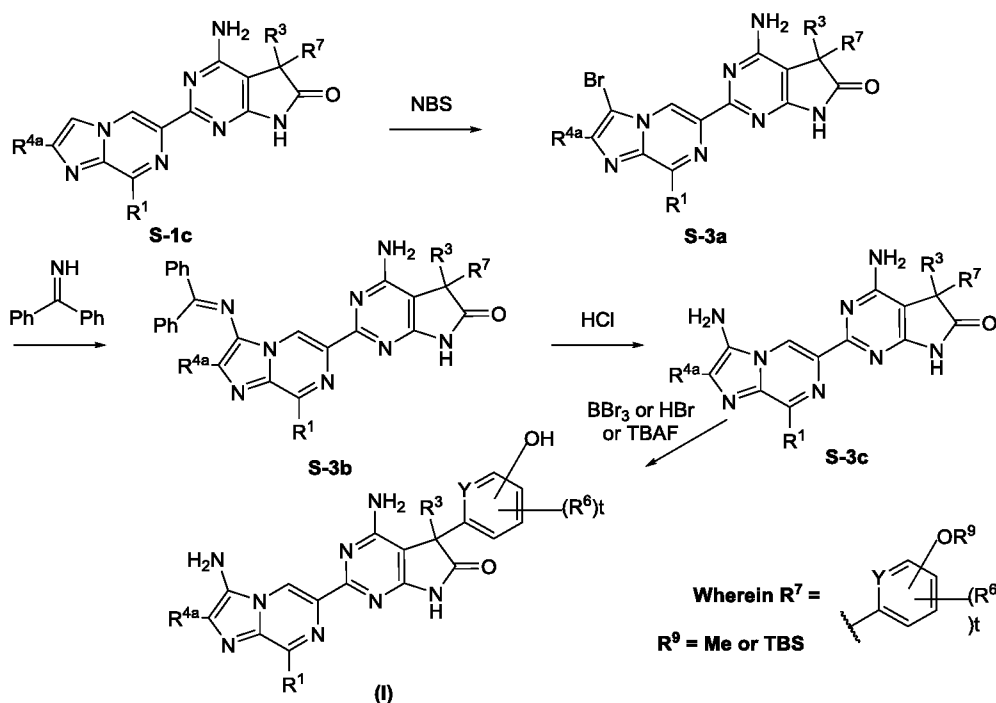
to the compounds of formula **S-2b**. Upon a treatment with an appropriate deprotecting agent such as BBr_3 , HBr or TBAF in a solvent such as DCM or THF , the intermediate **S-2b** yields compounds of structural Formula (I).

Scheme 2



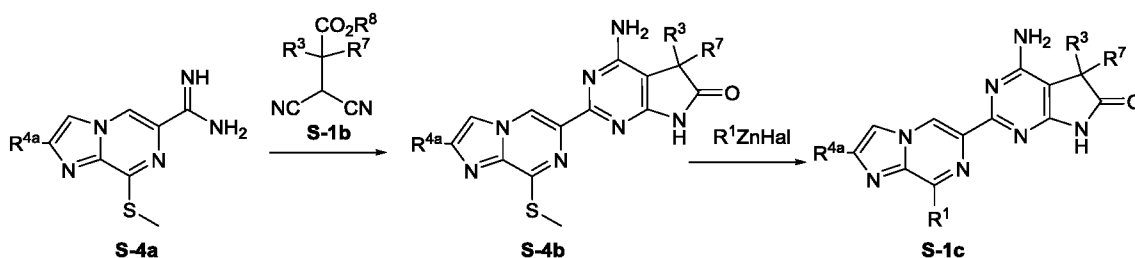
Compounds of Formula (I) where X is $\text{C}(\text{R}^{4b})$ and R^{4b} is NH_2 can be prepared as outlined in **Scheme 3**. Treatment of **S-1c** with a suitable halogenating agent such as NBS in a solvent such as DMF can provide the respective halogenated intermediate **S-3a**. Treatment of **S-3a** with imine such as diphenylmethanimine in a presence of a palladium catalyst such as 2nd generation XantPhos precatalyst and a base in a suitable solvent such as dioxane at elevated temperature results in the intermediate **S-3b**. Treatment of **S-3b** with HCl at RT in a suitable solvent system such as THF and water may result in the conversion of **S-3b** to compounds of the formula **S-3c**, which upon a deprotection with a proper deprotecting reagent such as BBr_3 or HBr or TBAF in a solvent such as DCM affords compounds of structural Formula (I).

Scheme 3



Advanced intermediate of the formula S-1c can be prepared as depicted in Scheme 4. The thiomethyl amidine intermediate S-4a can be cyclized with a suitable malononitrile reagent S-1b, utilizing the methods described in the Scheme 1, to afford the intermediate S-4b. Treatment of the S-4b with an appropriate alkylzinc reagent, R^1ZnHal , in a presence of a suitable palladium catalyst-ligand system such as Xantphos biaryl precatalyst, affords the compounds of formula S-1c.

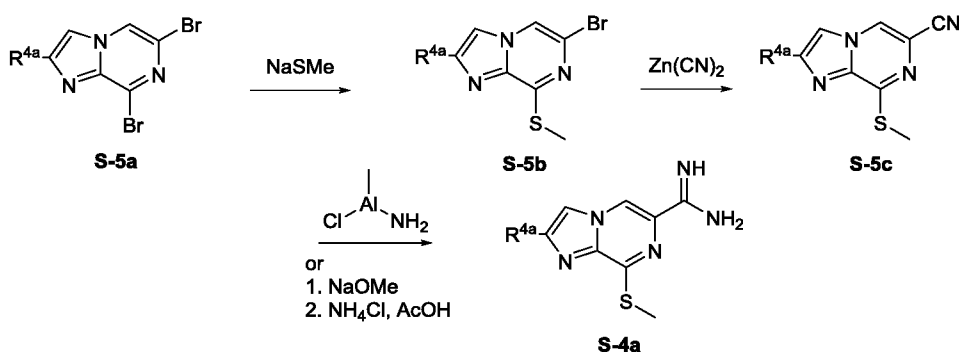
Scheme 4



Intermediates of the formula S-4a can be prepared by the sequence depicted in Scheme 5. Commercially available dibromo intermediate S-5a can be converted to the thiomethyl intermediate S-5b by a nucleophilic displacement using sodium thiomethoxide as described by Belanger, D. B. et al *Bioorg. Med. Chem. Lett.* **2010**, 20, 5170. Compound S-5c can be obtained by a treatment of the intermediate S-5b with a reagent such as $\text{Zn}(\text{CN})_2$ in a presence of a suitable palladium catalyst such as $\text{Pd}(\text{dppf})\text{Cl}_2$. Transformation of the thiomethyl nitrile intermediate S-5c into the amidine intermediate S-4a can be accomplished with a reagent such as amino(chloro)methylaluminum, prepared from trimethylaluminum and

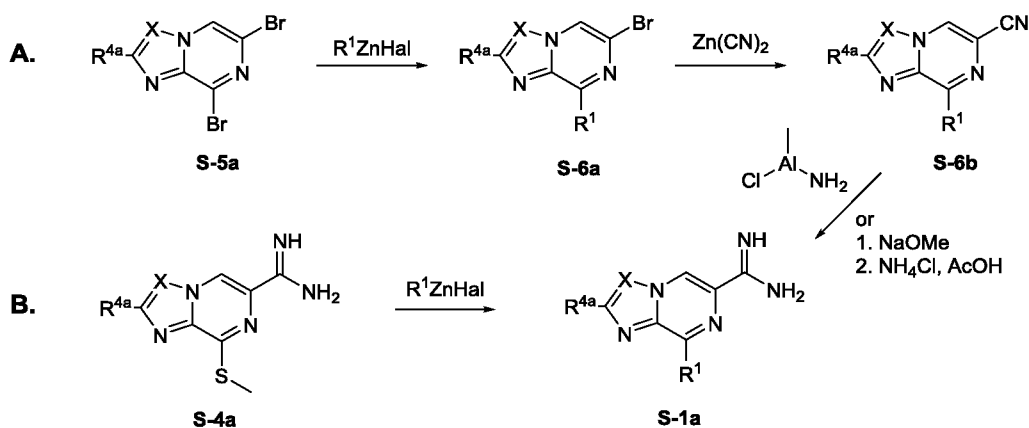
NH₄Cl, in a non-polar solvent such as toluene at elevated temperature as described by Garigipati, R. S. et al *Tetrahedron Letters* **1990**, 31(14), 1969. The nitrile **S-5c** can also be converted to the amidine **S-4a** by using sodium methoxide in methanol to form the imidate, which can then be transformed to the amidine **S-4a** using NH₄Cl and acetic acid as described by Pinner, A. et al, *Ber. Dtsch. Chem. Ges.* **1877**, 10, 1889.

Scheme 5



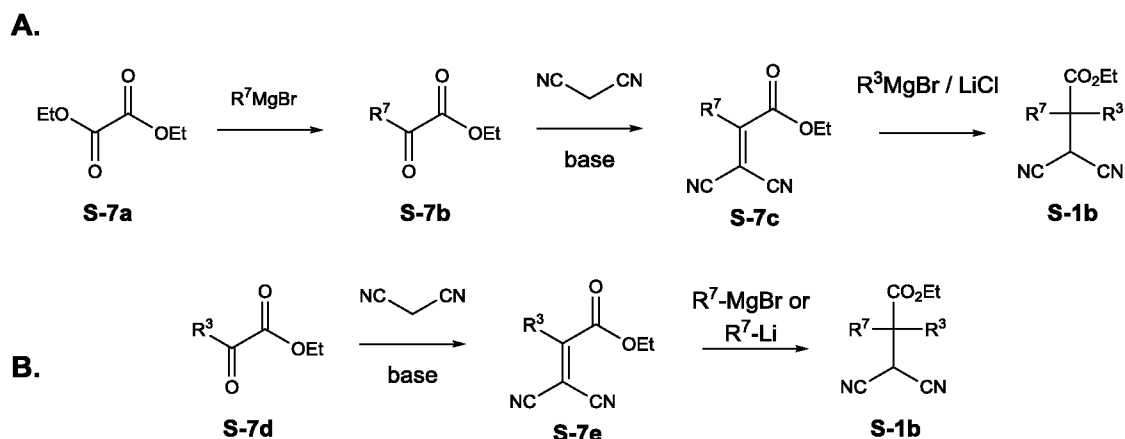
The amidine coupling partners of the formula **S-1a** can be prepared as outlined in **Scheme 6**, lines A and B. Commercially available dibromo intermediates of the formula **S-5a** can be selectively coupled to an alkylzinc reagent, R¹ZnHal, using a palladium catalyst such as Pd(PPh₃)₂Cl₂ to give the compound **S-6a**, which can be transformed into the nitrile intermediate **S-6b** using Zn(CN)₂ and a palladium catalyst such as Pd(dppf)Cl₂ at an elevated temperature. Transformation of the nitrile intermediate **S-6b** into the amidine intermediate **S-1a** can be accomplished with a reagent such as amino(chloro)methylaluminum or sodium methoxide, NH₄Cl and acetic acid in accordance with the literature references from **Scheme 5**. Alternatively, intermediates of the formula **S-1a** can be prepared when the amidine **S-4a** is treated with an appropriate alkylzinc reagent, R¹ZnHal, in a presence of a suitable catalyst-ligand system such as Xantphos biaryl precatalyst.

Scheme 6



Malononitrile type coupling partners such as **S-1b**, depicted as the ethyl ester, may be prepared as shown in **Scheme 7**, lines A and B. Thus, treatment of the diethyl oxalate **S-7a** with a suitable aryl magnesium bromide (with or without lithium chloride additive) or the lithiate of heteroaryl reagents derived from the bromide precursor via metal-halogen exchange in a suitable solvent such as THF affords the compound **S-7b**. Treatment of **S-7b** with malononitrile and a suitable base such as piperidine in a solvent such as EtOH at an elevated temperature affords the compound **S-7c** which, upon a treatment with a suitable alkyl magnesium bromide (with or without lithium chloride additive) in a solvent such as THF, affords the malononitrile **S-1b**. Alternatively, a malononitrile type coupling partners can be assembled as outlined in **Scheme 7**, line B. Commercially available intermediate **S-7d** ($R^3 = \text{Me}$), can undergo condensation with malononitrile, as described in the literature by Hagiwara *et al. Synthesis* **1974**, 9, 669 to afford intermediate **S-7e**. Subsequent 1,4-addition with a Grignard reagent or lithiate in a solvent such as THF at a temperatures ranging from -78°C to a RT affords the functionalized malononitrile **S-1b**.

Scheme 7



Compounds of the present invention possess an asymmetric center at the carbon bearing the R^3 and R^7 substituents which can have either the R or S configuration. These enantiomeric mixtures may be separated or resolved to single enantiomers using chiral SFC chromatography. Racemic material can be resolved to enantiomerically pure compounds at the final step, or one of the earlier steps in the route. For example, intermediates of formula **S-1b** can undergo chiral resolution to afford enantiopure isomers that may be carried on in the coupling with amidines to afford enantiomerically pure compounds of formula **S-1c**. Alternatively, enantiomeric resolution can be performed post formation of general intermediate **S-1c** or **S-2a**. Also, a chiral resolution of the intermediate **S-2b** may be required if a second asymmetric center is introduced to the enantiopure intermediate **S-1c** during its transformation into **S-2b** as outlined in **Scheme 2**. Unless otherwise noted, the examples in

the present invention are enantiomerically pure isomers (*R* or *S*). Biochemical assay data is listed for the more active enantiomer if only one of the enantiomers is active.

The independent synthesis of diastereomers and enantiomers or their chromatographic separations may be achieved using methods familiar to those skilled in the art and by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by X-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute stereochemistry, or by vibrational circular dichroism (VCD) spectroscopy.

Throughout the synthetic schemes and examples, abbreviations and acronyms may be used with the following meanings unless otherwise indicated:

AIBN = 2,2'-azobisisobutyronitrile; anhydr. = anhydrous; aq. = aqueous; bp, b.p. = boiling point; br s = broad singlet; BBr₃ = tribromoborane; Bu = butyl; *t*-Bu = *tert*-butyl; BuLi = butyllithium; *t*-BuOH, *tert*-BuOH = *tert*-butanol; *t*BuOK = potassium *tert*-butoxide; CDCl₃ = deuterated chloroform; CD₃OD = tetradeuteromethanol; CELITE = diatomaceous earth; CF₃ = trifluoromethyl; cGMP = cyclic guanosine monophosphate; conc, conc. = concentrated, concentrate, concentrates; DBU = 1,8-Diazabicyclo[4.3.0]undec-7-ene; DCM = dichloromethane; 1,2- DCE, DCE = 1,2-dichloroethane; DETA-NO = Diethylenetriamine/nitric oxide adduct; DMA, DMAC = *N,N*,-dimethylacetamide; DMF = *N,N*-dimethylformamide; DMSO = dimethylsulfoxide; DMSO *d*-6 = deuterated dimethylsulfoxide; dppf = 1,1'-bis(diphenylphosphino)ferrocene; DTT = dithiothreitol; EAB = egg albumin; EBSS = Earle's balanced salt solution; equiv, eq. = equivalent(s); Et = ethyl; Et₃N = triethylamine; EtOAc = ethyl acetate; EtOH = Etanol; GTP = guanosine triphosphate; h, hr = hour; Hal = halogen; HCl = hydrochloric acid; HPLC = high pressure liquid chromatography; HTRF = homogeneous time resolved fluorescence; Int. = intermediate; *i*Pr = isopropyl; IP = inflection points; IPA, *i*-PrOH = isopropanol; LCMS, LC/MS = liquid chromatography-mass spectrometry; LDA = lithium diisopropylamide; LiHMDS, LHMDS = lithium bis(trimethylsilyl)amide; min, min. = minute; M = Molar; Me = methyl; MeCN, ACN = acetonitrile; MeI = methyl iodide; MeOH = methanol; mp, m.p. = melting point; mpk = milligrams per kilogram; N = Normal; N₂ = nitrogen; NaOMe = sodium methoxide; NCS = *N*-chloro succinimide; NBS = *N*-bromo succinimide; NaHMDS = sodium bis(trimethylsilyl)amide; NaHCO₃ = sodium bicarbonate; NH₄Cl = ammonium chloride; NMR = nuclear magnetic resonance; N.D. = not determined; PDA = photodiode array;

$\text{Pd}_2(\text{dba})_3$ = tris(dibenzylideneacetone)dipalladium (0); Ph = phenyl; Pr = propyl; psig = pounds per square inch gauge; PTLC, prep TLC = preparative thin layer chromatography; rac = racemic; rt = retention time; RP-HPLC = reverse phase HPLC; RT = room temperature; sat., sat'd = saturated; SFC = supercritical fluid chromatography; sGC = soluble guanylate cyclase; TBAF = tetrabutylammonium fluoride; TFA = trifluoroacetic acid; TFAA = trifluoroacetic anhydride; TLC = thin layer chromatography; THF = tetrahydrofuran; VCD = vibrational circular dichroism; v, v/v = volume, volume to volume; w, w/w = weight, weight to weight.

Columns used in the chiral resolution of stereoisomers are set forth in the examples below as follows: AD = CHIRALPAK[®] AD; AD-H = CHIRALPAK[®] AD-H; AS = CHIRALPAK[®] AS; AS-H = CHIRALPAK[®] AS-H; IA = CHIRALPAK[®] IA; IC = CHIRALPAK[®] IC; OD-H = CHIRALCEL[®] OD-H; and OJ-H = CHIRALCEL[®] OJ-H.

The following examples are provided to more fully illustrate the present invention, and shall not be construed as limiting the scope in any manner. Unless stated otherwise, the following conditions were employed. All operations were carried out at room temperature or RT (RT), that is, at a temperature in the range 18-25°C. Reactions are generally done using commercially available anhydrous solvents under an inert atmosphere, either N₂ or argon. Microwave reactions were done using a BIOTAGE Initiator[™] or CEM EXPLORER[®] system. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (4.5-30 mmHg) with a bath temperature of up to 50°C. The course of reactions was followed by thin layer chromatography (TLC) and/or tandem high performance liquid chromatography (HPLC) followed by electron spray mass spectroscopy (MS), herein termed LCMS, and any reaction times are given for illustration only. The structure of all final compounds was assured by at least one of the following techniques: MS or proton nuclear magnetic resonance (¹H NMR) spectrometry, and the purity were assured by at least one of the following techniques: TLC or HPLC. ¹H NMR spectra were recorded on either a Varian Unity or a Varian Inova instrument at 300, 400, 500 or 600 MHz using the indicated solvent. ¹H NMR data are in the form of delta values for major diagnostic protons and are given in parts per million (ppm) relative to residual solvent peaks (multiplicity and number of hydrogen atoms). Conventional abbreviations used for signal shape are: s. singlet; d. doublet (apparent); t. triplet (apparent); m. multiplet; br. broad; etc. MS data were recorded on a Waters Micromass or WatersZQ unit, interfaced with a Hewlett-Packard (AGILENT 1100) HPLC instrument, and operating on MASSLYNX/OpenLynx software. Electrospray ionization was used with positive (ES+) or negative ion (ES-) detection; and diode array detection. Purification of compounds by preparative reverse phase HPLC was performed on a

GILSON system using a YMC-Pack Pro C18 column (150 x 20 mm i.d.) eluting at 20 mL/min with a water/MeCN (0.1% TFA) gradient (typically 5% MeCN to 95% MeCN) or using a SUNFIRE Prep C18 OBD 5 μ M column (100 x 30 mm i.d.) eluting at 50 mL/min with a water/MeCN (0.1% TFA) gradient. Purification of compounds by preparative mass triggered reverse phase HPLC was performed on Waters MS directed Preparative Scale HPLC. Purification of compounds by preparative thin layer chromatography (PTLC) was conducted on 20 x 20 cm glass plates coated with silica gel, commercially available from Analtech; or E. Merck. Flash column chromatography was carried out on a glass silica gel column using Kieselgel 60, 0.063-0.200 mm (SiO₂), or on a BIOTAGE SiO₂ cartridge system using the BIOTAGE Horizon and BIOTAGE SP-1 systems; or a Teledyne Isco SiO₂ cartridge using the COMBIFLASH Rf system. Chemical symbols have their usual meanings, and the following abbreviations have also been used: h or hr (hs), min (minutes), v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (litre(s)), mL (millilitres), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq or equiv (equivalent(s)), μ M (micromolar), nM (nanomolar), ca (circa/about).

The following are representative procedures for the preparation of intermediates used to prepare the final products described in the Examples that follow thereafter. These examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

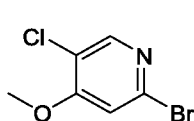
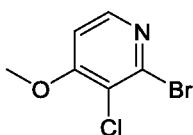
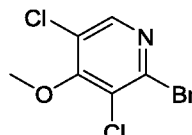
It is understood that a chiral center in a compound may exist in the "S" or "R" stereo-configurations, or as a mixture of both. In some of the examples for intermediate compounds and final compounds, such compounds having a racemic chiral center were separated into individual stereoisomers, for example, referred to as isomer A (or enantiomer A or the like), which refers to the observed faster eluting isomer, and isomer B (or enantiomer B or the like), which refers to the observed slower eluting isomer, and each such isomer may be noted in the example as either the fast or slow eluting isomer. When a single "A" or "B" isomer intermediate is used to prepare a downstream compound, the downstream compound may take the "A" or "B" designation that corresponds to the previously used intermediate.

Any intermediates described below may be referred to herein by their number preceded by "I-." For illustration, the racemic parent title compound would be referred to as **Intermediate 15 (I-15, or rac I-15)**, and the separated stereoisomers are noted as **Intermediates 15A and 15B (or I-15A and I-15B)**. In some examples, compounds having a chiral center were derived synthetically from a single isomer intermediate; *e.g.*, Example **13B** was made using stereoisomer **I-6B**. In some cases intermediates or examples contain more

than one chiral center. In such cases, the separation of isomers may require more than one chiral resolution. In such cases, the intermediate or example number can be followed by 2 letters (*e.g.* **Ex-108AB**). For these intermediates and examples, the first letter represents the A or B isomer from the first separation and the second letter represents the A or B isomer from the second separation. Absolute stereochemistry of separate stereoisomers in the Examples and Intermediates was not determined unless stated otherwise in an Example or Intermediate synthesis. An asterisk (*) may be used in a chemical structure drawing that indicates the location of a chiral center.

INTERMEDIATES 1, 2 and 3

2-bromo-5-chloro-4-methoxypyridine, 2-bromo-3-chloro-4-methoxypyridine and 2-bromo-3,5-dichloro-4-methoxypyridine

**I-1****I-2****I-3**

Step A- 5-chloro-4-methoxypyridin-2-amine, 3-chloro-4-methoxypyridin-2-amine and 3,5-dichloro-4-methoxypyridin-2-amine: To a flask containing 4-methoxypyridin-2-amine (40.0 g, 322 mmol) in MeCN (2 L) at 0 °C was added 1-chloropyrrolidine-2,5-dione (64.6 g, 484 mmol). The resulting mixture was stirred for 1.5 h at 0 °C. The reaction was quenched by the addition of sat. aq. sodium thiosulfate (1 L). The resulting mixture was extracted with EtOAc (3 x 500 mL) and the organic layers were combined, dried over anhydr. Na₂SO₄, filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by silica gel column chromatography with (EtOAc/EtOH = 3/1)/petroleum ether (10% to 50%) to afford 5-chloro-4-methoxypyridin-2-amine, 3-chloro-4-methoxypyridin-2-amine and 3,5-dichloro-4-methoxypyridin-2-amine.

Step B- 2-bromo-5-chloro-4-methoxypyridine: To a flask under an inert atmosphere of N₂, containing 5-chloro-4-methoxypyridin-2-amine (8.0 g, 50 mmol) and hydrobromic acid (67.2 mL, 500 mmol 40%) at 0 °C was added bromine (7.6 mL, 150 mmol) dropwise, followed by the dropwise addition of sodium nitrite (8.4 g, 125 mmol) in water (67 mL). The resulting mixture was stirred at 0 °C for 1 h. To this, dropwise was added sodium hydroxide (5.9 g, 150 mmol) in water (28 mL). The mixture was extracted with EtOAc (3 x 200 mL). The combined organic layer was dried over anhydr. Na₂SO₄, filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by silica gel column chromatography with EtOAc/petroleum ether (0-30%) to afford the title compound, 2-bromo-

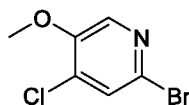
5-chloro-4-methoxypyridine, **I-1**. MS: 222, 224 ($M + 1$). ^1H NMR (CDCl_3 , 400 MHz): δ 8.24 (s, 1H), 7.05 (s, 1H), 3.99 (s, 3H).

INTERMEDIATE 2: 2-bromo-3-chloro-4-methoxypyridine was prepared via **Step B** using 3-chloro-4-methoxypyridin-2-amine as a starting material. **I-2**: MS 222, 224 ($M + 1$). ^1H NMR (CDCl_3 , 300 MHz): δ 8.18 (d, $J = 5.7$ Hz, 1H), 6.84 (d, $J = 5.7$ Hz, 1H), 3.98 (s, 3H).

INTERMEDIATE 3: 2-bromo-3,5-dichloro-4-methoxypyridine was prepared via **Step B** using 3,5-dichloro-4-methoxypyridin-2-amine as a starting material. **I-3**: MS 256, 258 ($M + 1$). ^1H NMR (CDCl_3 , 300 MHz): δ 8.28 (s, 1H), 4.04 (s, 3H).

INTERMEDIATE 4

2-bromo-4-chloro-5-methoxypyridine



Step A- 2-bromo-5-methoxypyridine 1-oxide: Into a flask were placed 2-bromo-5-methoxypyridine (20 g, 106 mmol), 3-chlorobenzoperoxoic acid (27.5 g, 160 mmol), and DCE (250 mL). The resulting mixture was stirred at 60 °C for 16 h. The reaction mixture was cooled, quenched by the addition of diethyl amine (10 mL) and concentrated *in vacuo*. The residue was purified by column chromatography with EtOAc/petroleum ether (50%~100%) to afford the title compound.

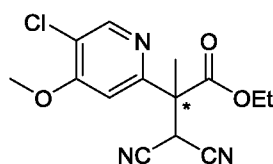
Step B- 2-bromo-5-methoxy-4-nitropyridine 1-oxide: To a flask, containing sulfuric acid (50 mL, 938 mmol) was added the intermediate from **Step A** (17 g, 83 mmol) followed by a dropwise addition of nitric acid (10 mL, 228 mmol). The temperature was raised to 90 °C then the mixture was cooled to 60 °C and the rest of nitric acid (40 mL, 910 mmol) was added. The resulting mixture was stirred at 60 °C for 10 min, then cooled and poured into ice/water mixture (1000 mL). The solid was collected by filtration, washed with MeCN (2 x 20 mL) and EtOAc (20 mL) and dried in an oven to afford the title compound.

Step C- 2-bromo-5-methoxypyridin-4-amine: Into a flask, containing the intermediate from **Step B** (10 g, 40.2 mmol), were placed iron powder (22.5 g, 403 mmol) and NH_4Cl (2.1 g, 39.3 mmol) in EtOH (75 mL)/water (25 mL) and the mixture was stirred at 70 °C for 1 h. The reaction mixture was filtered and the residue was washed with EtOH (3 x 50 mL). The combined filtrate was concentrated *in vacuo* to dryness. The residue was dissolved in EtOAc (100 mL), washed with water (20 mL) and brine (20 mL), dried over anhydr. Na_2SO_4 , and filtrated. The filtrate was concentrated *in vacuo* to afford the title compound.

Step D- 2-bromo-4-chloro-5-methoxypyridine: To a flask containing the intermediate from **Step C** (5 g, 24.63 mmol) and HCl (50 mL, 37%) at 0 °C was added dropwise a solution of sodium nitrite (1.78 g, 25.9 mmol) in water (10 mL). The resulting mixture was stirred at 0 °C for 15 min, then a solution of copper (I) chloride (2.93 g, 29.6 mmol) in HCl (100 mL, 37%) was added dropwise at 0 °C. The resulting mixture was stirred at RT for 2 h, then diluted with water (1000 mL). The solid was collected by filtration and washed with water (100 mL), then dissolved in EtOAc (100 mL), washed with sat., aq. NaHCO₃ (2 x 30 mL) and brine (100 mL), dried over anhydr. Na₂SO₄, and filtered through a silica gel pad. The filtrate was concentrated *in vacuo* to afford the title compound, **I-4**. MS: 222, 224 (M + 1). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.05 (s, 1H), 7.53 (s, 1H), 4.01 (s, 3H).

INTERMEDIATE 5, 5A and 5B

Ethyl 2-(5-chloro-4-methoxypyridin-2-yl)-3,3-dicyano-2-methylpropanoate and the S and R isomers thereof

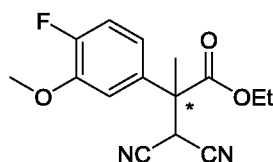


Ethyl 2-(5-chloro-4-methoxypyridin-2-yl)-3,3-dicyano-2-methylpropanoate: To a flask under an inert atmosphere of N₂, containing BuLi (12.6 mL, 31.4 mmol, 2.5 M in THF) in toluene (120 mL) at -78 °C was added dropwise 2-bromo-5-chloro-4-methoxypyridine (7.0 g, 31.4 mmol) in toluene (70 mL). The mixture was stirred at -78 °C for 30 min before a solution of ethyl 3,3-dicyano-2-methylacrylate (5.2 g, 31.4 mmol) in toluene (10 mL), prepared according to Hagiware *et al. Synthesis* **1974**, 9, 669, was added. The resulting mixture was stirred at -78 °C for 30 min and then quenched by the addition of sat. aq. NH₄Cl (300 mL). The resulting mixture was extracted with EtOAc (3 x 200 mL) and the combined organic layer was dried over anhydr. Na₂SO₄, filtered and the filtrate concentrated *in vacuo* to dryness. The residue was purified by column chromatography eluting with EtOAc/petroleum ether (5%~20%) to afford the racemic title compound **I-5**. The racemic material was resolved using chiral Prep-SFC (CHIRALPAK AD-H) to afford isomers **I-5A** (faster eluting) and **I-5B** (slower eluting). MS: 308 (M + 1). ¹H NMR (CDCl₃, 300 MHz): δ 8.41 (s, 1H), 7.01 (s, 1H), 5.20 (s, 1H), 4.18-4.32 (m, 2H), 4.01 (s, 3H), 2.00 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H).

INTERMEDIATE 6, 6A and 6B

Ethyl 3,3-dicyano-2-(4-fluoro-3-methoxyphenyl)-2-methylpropanoate and the S and R isomers thereof

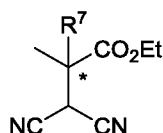
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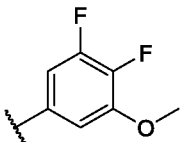
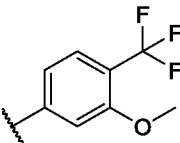
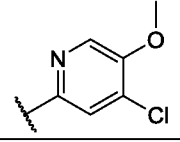
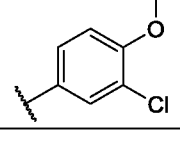
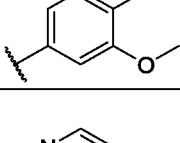
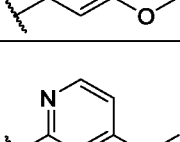
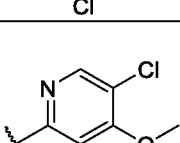
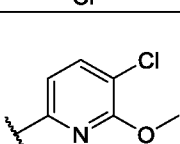
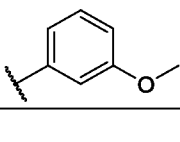
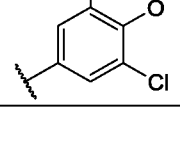
Into a flask under an inert atmosphere of N_2 , were placed magnesium (0.35 g, 14.40 mmol) and iodine (0.31 g, 1.22 mmol) in THF (5 mL). A solution of 4-bromo-1-fluoro-2-methoxybenzene (2.5 g, 12.19 mmol) in THF (20 mL) was added dropwise over 10 min, maintaining the reaction temperature at reflux. The reaction mixture was stirred at reflux for 1 h, then cooled to RT. Lithium chloride (0.56 g, 13.21 mmol) was added and the mixture was stirred at RT for 30 min, then cooled to $-20\text{ }^\circ\text{C}$. A solution of ethyl 3,3-dicyano-2-methylprop-2-enoate (1.8 g, 10.96 mmol) in THF (25 mL), prepared according to Hagiware *et al. Synthesis* **1974**, 9, 669, was added dropwise at $-20\text{ }^\circ\text{C}$. The resulting solution was stirred at $0\text{ }^\circ\text{C}$ for 1 h, then quenched by the addition of sat. aq. NH_4Cl (100 mL). The resulting solution was extracted with EtOAc (2 x 100 mL) and the organic layers combined, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo* to dryness and the residue was purified by column chromatography with EtOAc/petroleum ether (1/20) to afford the racemic title compound **I-6**. The racemic material was resolved using chiral Prep-SFC (CHIRALPAK AS-H) to afford isomers **I-6A** (faster eluting) and **I-6B** (slower eluting). MS: 289 (M - 1). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.16-7.09 (m, 1H), 6.96-6.89 (m, 2H), 4.45 (s, 1H), 4.34-4.23 (m, 2H), 3.91 (s, 3H), 1.98 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H).

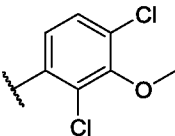
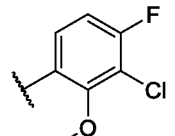
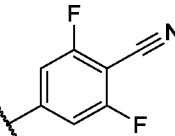
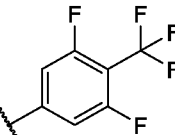
Using a similar procedure to that described for the synthesis of intermediate **I-5** or **I-6**, the following compounds listed in **Table 1** were prepared using commercially available starting reagents or from compounds known in the literature.

Table 1



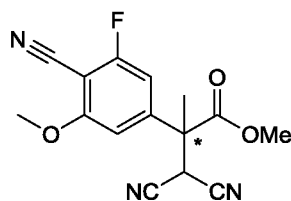
Int.	Chiral Resolution Column	R^7	MS (M - 1) or ^1H NMR
I-7A I-7B	CHIRALPAK AD-H		323 (M - 1)

I-8A I-8B	CHIRALPAK AD-H		307 (M - 1)
I-9A I-9B	CHIRALPAK AD-H		339 (M - 1)
I-10A I-10B	CHIRALPAK IA		306 (M - 1)
I-11A I-11B	CHIRALPAK IA		305 (M - 1)
I-12A I-12B	CHIRALPAK AS-H		305 (M - 1)
I-13	RACEMIC		372 (M - 1) 374 (M + 1)
I-14	RACEMIC		306 (M - 1)
I-15A I-15B	CHIRALPAK AD-H		340 (M - 1)
I-16A I-16B	CHIRAL ART Cellulose-SB		308 (M + 1)
I-17A I-17B	CHIRALPAK IA		271 (M - 1)
I-18	RACEMIC		339 (M - 1)

I-19A I-19B	CHIRALPAK IF		339 (M - 1)
I-20A I-20B	CHIRALPAK AD-H		¹ H NMR (300 MHz, CDCl ₃) δ 7.32 (dd, <i>J</i> = 8.7, 8.7 Hz, 1H), 6.84 (dd, <i>J</i> = 1.2, 8.7 Hz, 1H), 4.57 (s, 1H), 4.36-4.27 (m, 2H), 3.96 (s, 3H), 2.00 (s, 3H), 1.27 (t, <i>J</i> = 7.2 Hz, 3H); MS 323 (M - 1).
I-21	RACEMIC		302 (M - 1)
I-22	RACEMIC		¹ H NMR (400 MHz, DMSO-d ₆) δ 7.55 (d, <i>J</i> = 11.4 Hz, 2H), 5.89 (s, 1H), 4.29 (q, <i>J</i> = 7.1 Hz, 2H), 1.88 (s, 3H), 1.19 (t, <i>J</i> = 7.1 Hz, 3H).

INTERMEDIATE 23, 23A and 23B

Methyl 3,3-dicyano-2-(4-cyano-3-fluoro-5-methoxyphenyl)-2-methylpropanoate and the S and R isomers thereof



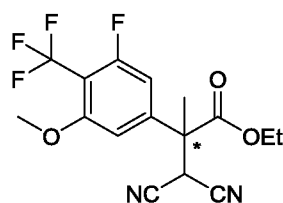
5

Into a flask, containing **I-21** (500 mg, 1.65 mmol) in THF (50 mL) at 0 °C was added dropwise sodium methoxide (891 mg, 4.12 mmol, 25% in MeOH). The resulting mixture was stirred at RT for 16 h, then quenched by the addition of sat. aq. NH₄Cl (100 mL). The resulting solution was extracted with EtOAc (3 x 50 mL) and the combined organic layer was

10

dried over anhydr. Na₂SO₄, filtered and the filtrate concentrated *in vacuo* to dryness. The residue was purified by column chromatography with EtOAc/petroleum ether (10%-50%) to afford the title compound **I-23**. The racemic material was resolved using chiral SFC (CHIRALPAK AD-H) to afford isomers **I-23A** (faster eluting) and **I-23B** (slower eluting) of the title compound. MS: 300 (M - 1). ¹H NMR (CDCl₃, 300 MHz): δ 6.83 (dd, *J* = 1.8, 9.3 Hz, 1H), 6.75 (dd, *J* = 1.2, 1.2 Hz, 1H), 4.48 (s, 1H), 4.00 (s, 3H), 3.86 (s, 3H), 2.01 (s, 3H).

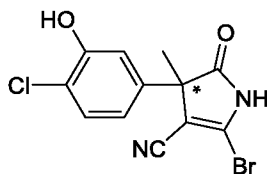
15

INTERMEDIATE 24, 24A and 24B

Using essentially the same procedure to that described in the synthesis of **I-23**, intermediate **I-24** was prepared using **I-22** as the starting material. The racemic material was resolved using chiral SFC (CHIRALPAK AS) to afford isomers **I-24A** (faster eluting) and **I-24B** (slower eluting) of the title compound. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 7.10 (d, *J* = 12.8 Hz, 1H), 7.02 (s, 1H), 5.92 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.93 (s, 3H), 1.86 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

INTERMEDIATE 25A

2-bromo-4-(4-chloro-3-hydroxyphenyl)-4-methyl-5-oxo-4,5-dihydro-1H-pyrrole-3-carbonitrile

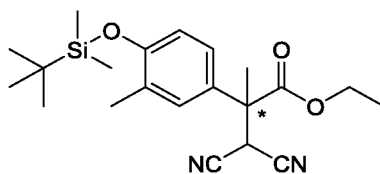


2-bromo-4-(4-chloro-3-hydroxyphenyl)-4-methyl-5-oxo-4,5-dihydro-1H-pyrrole-3-carbonitrile:

To a flask containing **I-12A** (200 mg, 0.65 mmol) in DCM (6 mL) at 0 °C was added dropwise BBr₃ (0.6 mL, 6.52 mmol). The resulting mixture was stirred at 0 °C for 1 h and at RT for 16 h. The reaction was quenched by the addition of sat. aq. NaHCO₃ (100 mL). The resulting solution was extracted with EtOAc (3 x 100 mL), the combined organic layer was dried over anhydr. Na₂SO₄, filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by column chromatography with EtOAc/petroleum ether (20%~50%) to afford the title compound **I-25A**. MS: 325, 327 (*M* - 1). ¹H NMR (CDCl₃, 400 MHz): δ 7.61 (br s, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.90 (dd, *J* = 2.0, 8.4 Hz, 1H), 5.63 (br s, 1H), 1.77 (s, 3H).

INTERMEDIATE 26, 26A and 26B

Ethyl 2-(4-((*tert*-butyldimethylsilyl)oxy)-3-methylphenyl)-3,3-dicyano-2-methylpropanoate and the *S* and *R* isomers thereof



Step A- (4-bromo-2-methylphenoxy)(tert-butyl)dimethylsilane: To a flask containing 4-bromo-2-methylphenol (10.0 g, 53.5 mmol), *tert*-butylchlorodimethylsilane (7.25 g, 48.1 mmol) in DCM (300 mL) at RT was added, in portions, 1*H*-imidazole (7.28 g, 107 mmol). The mixture was stirred at RT for 16 h, then quenched by the addition of water (50 mL). The organic layer was washed with sodium hydroxide (0.1 N, 50 mL x 3), water (50 mL) and brine (50 mL), dried over anhydr. Na₂SO₄, filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by column chromatography with petroleum ether to afford the title compound.

Step B- Ethyl 2-(4-((*tert*-butyldimethylsilyl)oxy)-3-methylphenyl)-2-oxoacetate: To a flask under an inert atmosphere of N₂, containing magnesium (0.20 g, 8.63 mmol), iodine (0.10 g, 0.332 mmol) and THF (2 mL) was added dropwise to a solution of intermediate from **Step A** (2.00 g, 6.64 mmol) in THF (8 mL). The reaction mixture was stirred at reflux for 1 h, then allowed to cool to RT.

To a separate flask, under an inert atmosphere of N₂, containing diethyl oxalate (1.16 g, 7.97 mmol) in THF (10 mL) at 0 °C was added dropwise the Grignard reagent prepared above. The resulting mixture was stirred at RT for 1 h then quenched by the addition of sat. aq. NH₄Cl (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over anhydr. Na₂SO₄, filtered and the filtrate concentrated *in vacuo* to dryness. The residue was purified by column chromatography with petroleum ether/EtOAc (5/1) to afford the title compound.

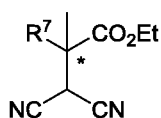
Step C- Ethyl 2-(4-((*tert*-butyldimethylsilyl)oxy)-3-methylphenyl)-3,3-dicyanoacrylate: Into a flask under an inert atmosphere of N₂, containing the intermediate from **Step B** (500 mg, 1.55 mmol) and malononitrile (307 mg, 4.65 mmol) in EtOH (10 mL) was added piperidine (13.20 mg, 0.155 mmol). The resulting mixture was stirred at 90 °C for 16 h, then concentrated *in vacuo* to dryness and the residue was purified by column chromatography with petroleum ether/EtOAc (5/1) to afford the title compound.

Step D –Ethyl 2-(4-((*tert*-butyldimethylsilyl)oxy)-3-methylphenyl)-3,3-dicyano-2-methylpropanoate: Into a flask under an inert atmosphere of N₂, were placed intermediate from **Step C** (570 mg, 1.54 mmol), lithium chloride (130 mg, 3.08 mmol) and THF (10 mL). The resulting mixture was stirred at RT for 0.5 h, then cooled to 0 °C and methylmagnesium bromide (2.31 mL, 2.31 mmol, 1 M in THF) was added dropwise. The resulting mixture was stirred at RT for 1 h, then quenched by the addition of sat. aq. NH₄Cl (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over anhydr. Na₂SO₄, filtered and the filtrate concentrated *in vacuo* to dryness. The residue was purified by column

chromatography with petroleum ether/EtOAc (5/1) to afford the title compound **I-26**. The racemic material was resolved using chiral SFC ((*R,R*)-WHELK-O) to afford isomers **I-26A** (faster eluting) and **I-26B** (slower eluting) of the title compound. MS: 385 (M - 1). ¹H NMR (400 MHz, CDCl₃) δ 7.12 (d, *J* = 2.8 Hz, 1H), 7.07 (dd, *J* = 2.8, 8.4 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 4.47 (s, 1H), 4.34–4.23 (m, 2H), 2.23 (s, 3H), 1.97 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.03 (s, 9H), 0.25 (s, 6H).

Using a similar procedure to that described for the synthesis of intermediate **I-26**, the following compounds in **Table 2** were prepared using either commercial starting reagents or from compounds known in the literature. Some intermediates were commercially available at **Step B** and the synthesis could commence at **Step C**.

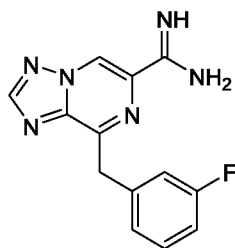
Table 2



Int.	Chiral Resolution Column	R ⁷	MS (M - 1)
I-27	RACEMIC		385 (M - 1)
I-28A I-28B	CHIRALPAK IA		289 (M - 1)
I-29A I-29B	CHIRALCEL OJ-H		271 (M - 1)

INTERMEDIATE A1

8-(3-fluorobenzyl)-[1,2,4]triazolo[1,5-a]pyrazine-6-carboximidamide



Step A- (3-Fluorobenzyl)zinc(II) bromide: To a flask under an inert atmosphere of N₂, containing zinc (2.8 g, 43.2 mmol) in THF (50 mL), was added 1,2-dibromoethane (0.2 g, 1.1 mmol), dropwise at 50 °C. The mixture was stirred at 50 °C for 10 min then chlorotrimethylsilane (0.14 mL, 1.1 mmol) was added dropwise at 50 °C. The mixture was allowed to cool to RT for 10 min then cooled to 0 °C for the addition of 1-(bromomethyl)-3-fluorobenzene (5.3 g, 28.1 mmol). The resulting mixture was stirred for 15 min at 0 °C then at RT 2 h. This resulted in the zinc reagent which was used for the next step.

Step B- 6-bromo-8-(3-fluorobenzyl)-[1,2,4]triazolo[1,5-a]pyrazine: Into a flask under an inert atmosphere of N₂, were placed 6,8-dibromo-[1,2,4]triazolo[1,5-a]pyrazine (6.0 g, 21.6 mmol) and bis(triphenylphosphine)palladium(II) dichloride (1.5 g, 2.2 mmol). To this was added the zinc reagent from **Step A**, and the mixture was stirred at RT for 16 h. The mixture was quenched by the addition of sat. aq. NH₄Cl (200 mL), and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydr. Na₂SO₄, filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by column chromatography with EtOAc/petroleum ether (1/5) to afford the title compound.

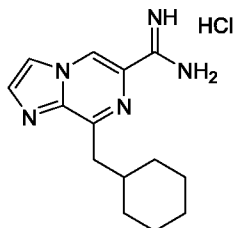
Step C- 8-(3-fluorobenzyl)-[1,2,4]triazolo[1,5-a]pyrazine-6-carbonitrile: Into a flask under an inert atmosphere of N₂, were placed intermediate from **Step B** (5.2 g, 16.9 mmol), Pd₂(dba)₃ (1.5 g, 1.7 mmol), dppf (1.9 g, 3.4 mmol), zinc (0.5 g, 8.4 mmol), zinc cyanide (2.6 g, 22.0 mmol) and DMA (60 mL). The resulting mixture was stirred at 120 °C for 1 h, then diluted with EtOAc (500 mL) and washed with water (3 x 250 mL) and brine (2 x 250 mL). The combined organic layer was dried over anhydr. Na₂SO₄, filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by column chromatography with EtOAc/petroleum ether (0-50%) to afford the title compound.

Step D- 8-(3-fluorobenzyl)-[1,2,4]triazolo[1,5-a]pyrazine-6-carboximidamide: Into a flask under an inert atmosphere of N₂, containing NH₄Cl (5.5 g, 103.0 mmol) in toluene (100 mL) at 0 °C was added dropwise trimethylaluminum (41 mL, 82.4 mmol). The resulting mixture was stirred at RT for 1 h, then intermediate from **Step C** (2.6 g, 10.3 mmol) was added. The resulting mixture was stirred at 100 °C for 1 h, cooled to 0 °C and quenched by the addition of DCM/MeOH mixture (1:1, 500 mL). The resulting mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in EtOAc (500 mL) and the basicity of the solution was adjusted to pH10 with sodium hydroxide (1 N). The resulting solution was extracted with EtOAc (3 x 200 mL) and the combined organic layer was dried over anhydr. Na₂SO₄, filtered and the filtrate concentrated *in vacuo* to dryness to afford the

title compound, **I-A1**. MS: 271 ($M + 1$). ^1H NMR ($\text{DMSO-}d_6$, 300 MHz): δ 9.43 (s, 1H), 8.80 (s, 1H), 7.36-7.26 (m, 3H), 7.08-7.04 (m, 1H), 4.57 (s, 2H).

INTERMEDIATE A2

8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazine-6-carboximidamide hydrochloride



Step A- (cyclohexylmethyl)zinc(II) iodide: Into a flask under an inert atmosphere of N_2 , were placed zinc (2.46 g, 37.6 mmol), DMF (35 mL) and (iodomethyl)cyclohexane (4.21 g, 18.78 mmol). To this was added a solution of diiodine (0.22 g, 0.87 mmol) in DMF (5 mL) at RT. The mixture was stirred at 80 °C for 3 h. This resulted in the zinc reagent solution which was used in the next step.

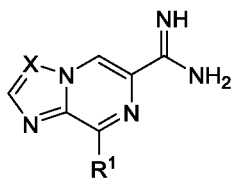
Step B- 6-bromo-8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazine: Into a flask under an inert atmosphere of N_2 , were placed 6,8-dibromoimidazo[1,2-*a*]pyrazine (4 g, 14.44 mmol), bis(triphenylphosphine)palladium(II) dichloride (1.01 g, 1.444 mmol) and THF (120 mL). The resulting mixture was stirred at RT for 1 h before the zinc reagent solution from **Step A** was added dropwise at 0 °C. The resulting mixture was stirred at RT for 16 h then quenched by the addition of sat. aq. NH_4Cl (400 mL). The resulting mixture was extracted with EtOAc (3 x 200 mL). The combined organic layer was washed with brine (2 x 500 mL), dried over anhydr. Na_2SO_4 , filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by column chromatography with EtOAc/petroleum ether (5%-45%) to afford the title compound.

Step C- 8-(cyclohexylmethyl)imidazo[1,2-*a*]pyrazine-6-carbonitrile: Into a flask under an inert atmosphere of N_2 , were placed intermediate from **Step B** (2.50 g, 8.50 mmol), dicyanozinc (0.70 g, 5.95 mmol), dppf (0.47 g, 0.850 mmol), $\text{Pd}_2(\text{dba})_3$ (0.440 g, 0.425 mmol), zinc (0.28 g, 4.25 mmol) and DMF (25 mL) and the resulting mixture was stirred at 120 °C for 1 h. The reaction was cooled to RT, quenched by the addition of water (250 mL) and EtOAc (250 mL). The resulting mixture was filtered and the filtrate was extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with brine (2 x 200 mL), dried over anhydr. Na_2SO_4 , filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by column chromatography eluting with EtOAc/petroleum ether (10%-60%) to afford the title compound.

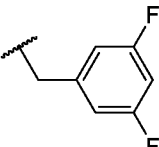
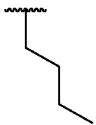
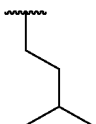
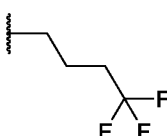
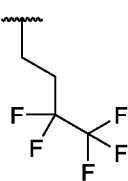
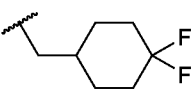
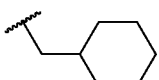
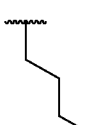
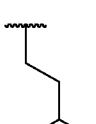
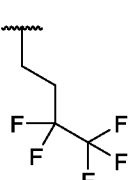
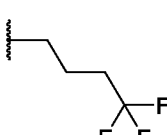
Step D- 8-(cyclohexylmethyl)imidazo[1,2-a]pyrazine-6-carboximidamide hydrochloride:

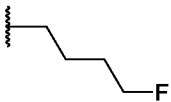
Into a flask under an inert atmosphere of N₂, were placed NaOMe (1.62 g, 30.0 mmol, 25%) in MeOH (30 mL) and intermediate from **Step C** (1.80 g, 7.49 mmol). The resulting mixture was stirred for at RT for 16 h then NH₄Cl (2.0 g, 37.5 mmol) was added. The resulting mixture was stirred at 70 °C for 3 h, then cooled to RT and diluted with THF (40 mL). The solid was filtered out and the filtrate was concentrated *in vacuo* to dryness. The residue was washed with THF (2 x 30 mL) and dried in the air to afford the title compound, **I-A2**. MS: 258 (M - HCl + 1). ¹H NMR (300 MHz, CD₃OD) δ 9.32 (s, 1H), 8.19 (s, 1H), 7.89 (d, *J* = 1.2 Hz, 1H), 3.12 (d, *J* = 7.2 Hz, 2H), 2.19-2.06 (m, 1H), 1.72-1.59 (m, 5H), 1.30-1.05 (m, 5H).

Using a similar procedure to that described for the preparation of intermediates **I-A1** and **I-A2**, the following intermediates in the **Table 3** were prepared either from a commercially available starting reagents or from compounds known in the literature. The intermediates in **Table 3** might be prepared as salts or as free bases.

Table 3

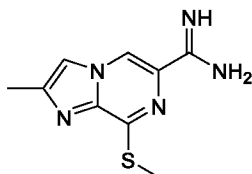
Int.	X	R ¹	MS (M + 1)
I-A3	C(H)		270
I-A4	C(H)		270
I-A5	C(H)		270
I-A6	N		271
I-A7	N		271

I-A8	N		289
I-A9	C(H)		218
I-A10	C(H)		232
I-A11	C(H)		272
I-A12	C(H)		308
I-A13	C(H)		294
I-A14	N		259
I-A15	N		219
I-A16	N		233
I-A17	N		309
I-A18	N		273

I-A19	N		237
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INTERMEDIATE A20

2-methyl-8-(methylthio)imidazo[1,2-a]pyrazine-6-carboximidamide

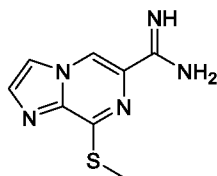


- 5 **Step A- 6-bromo-2-methyl-8-(methylthio)imidazo[1,2-a]pyrazine:** To a solution of 6,8-dibromo-2-methylimidazo[1,2-a]pyrazine (1.65 g, 5.67 mmol) in MeCN (17.2 mL) was slowly added sodium methanethiolate (0.48 g, 6.81 mmol) and the reaction mixture was stirred at RT overnight. The reaction mixture was concentrated *in vacuo* to afford the title compound that was used in the next step without purification.
- 10 **Step B- 2-methyl-8-(methylthio)imidazo[1,2-a]pyrazine-6-carbonitrile:** Into a flask under an inert atmosphere of N₂, were placed intermediate from **Step A** (1.3 g, 5.04 mmol) in DMA (10.1 mL), dppf (0.56 g, 1.01 mmol), Pd₂(dba)₃ (0.92 g, 1.01 mmol), zinc cyanide (0.65 g, 5.54 mmol) and zinc (0.17 g, 2.52 mmol). The reaction mixture was stirred at 70 °C
- 15 200 mL). The combined organic layer was dried over anhydr. Na₂SO₄, filtered and the filtrate concentrated *in vacuo* to dryness. The residue was purified by column chromatography eluting with Hexane/(EtOAc/EtOH 3:1) (0-50%) to afford the title compound.
- Step C- 2-methyl-8-(methylthio)imidazo[1,2-a]pyrazine-6-carboximidamide:** A solution of trimethylaluminum (9.42 mL, 18.85 mmol, 2 M toluene) was added dropwise at 0°C to a
- 20 solution of NH₄Cl (1.00 g, 18.85 mmol) in toluene (18.8 mL). The reaction mixture was warmed to RT over 1 h. Intermediate from **Step B** (0.77 g, 3.77 mmol) in toluene (0.4 mL) was added to the above mixture and it was heated at 100 °C for 2 h. Upon completion, the reaction mixture was diluted with DCM/MeOH mixture (1:1) (50 mL) and stirred vigorously for 1 h. The resulting mixture was filtered and washed with DCM/MeOH (1:1) (2 x 50 mL)
- 25 and the filtrate concentrated *in vacuo* to afford the title compound, **I-A20**. MS: 222 (M + 1).

INTERMEDIATE A21

8-(methylthio)imidazo[1,2-a]pyrazine-6-carboximidamide

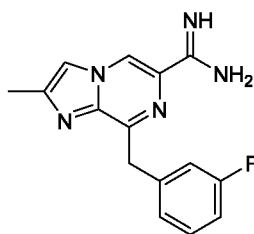
73



Intermediate **A21** was prepared using the same procedure as one described for the preparation of Intermediate **A20** using 6,8-dibromoimidazo[1,2-a]pyrazine as a starting material. MS: 208 (M + 1). ¹H NMR (400 MHz, DMSO *d*-6) δ 9.46 (s, 1H), 9.43 (b s, 1H), 8.28 (s, 1H), 7.82 (s, 1H), 2.70 (s, 3H).

INTERMEDIATE A22

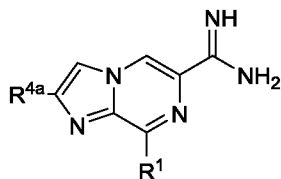
8-(3-fluorobenzyl)-2-methylimidazo[1,2-a]pyrazine-6-carboximidamide:



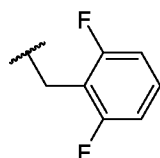
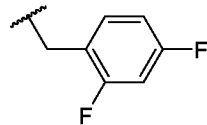
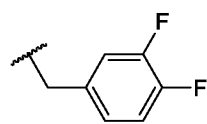
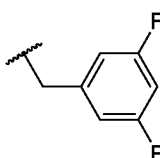
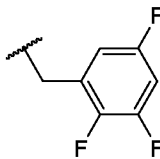
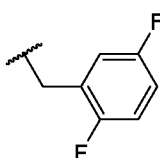
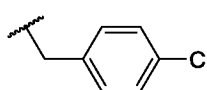
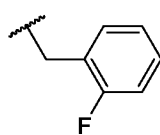
8-(3-fluorobenzyl)-2-methylimidazo[1,2-a]pyrazine-6-carboximidamide: Into a flask under an inert atmosphere of N₂, were placed **I-A20** (200 mg, 0.90 mmol), Xantphos generation II precatalyst (71 mg, 0.09 mmol), and (3-fluorobenzyl)zinc(II) chloride (9.0 mL, 4.52 mmol, 0.5 M THF). The reaction was warmed at 50 °C for 4 h then cooled, diluted with EtOAc, and passed through a pad of CELITE. The filtrate was dried over anhydr. Na₂SO₄, and concentrated *in vacuo* to dryness. The crude residue was purified by column chromatography eluting with DCM/MeOH (0-10%) to afford the title compound, **I-A22**. MS: 284 (M + H).

Using essentially the same procedure as one described for the preparation of intermediate **A22**, the following intermediates in **Table 4** were prepared from a commercially available starting reagents using either **I-A20** or **I-A21** as a starting material.

Table 4

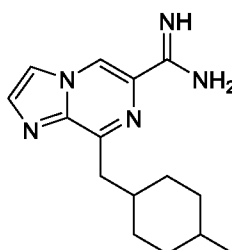


Int.	R ¹	R ^{4a}	MS (M + 1)
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I-A23		H	288
I-A24		H	288
I-A25		H	288
I-A26		H	288
I-A27		H	306
I-A28		H	288
I-A29		H	286
I-A30		Me	284

INTERMEDIATE A31

8-[(4-methylcyclohexyl)methyl]imidazo[1,2-a]pyrazine-6-carboximidamide



Step A- 1-(iodomethyl)-4-methylcyclohexane: To a solution of (4-methylcyclohexyl)methyl 4-methylbenzenesulfonate (0.6 g, 2.13 mmol) in DMF (3 mL), potassium iodide (3.5 g, 21.3 mmol) was added and the reaction mixture was stirred at 60 °C for 3 h, then cooled to RT and diluted with water (100 mL). The mixture was extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydr. Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography eluting with petroleum ether to afford the title compound.

Step B- 6-bromo-8-[(4-methylcyclohexyl)methyl]imidazo[1,2-*a*]pyrazine: Into a flask under an inert atmosphere of argon, were placed 4,7-diphenyl-1,10-phenanthroline (108 mg, 0.33 mmol), intermediate from **Step A** (774 mg, 3.25 mmol), nickel(II) iodide (203 mg, 0.65 mmol), 6,8-dibromoimidazo[1,2-*a*]pyrazine (600 mg, 2.167 mmol), and manganese (357 mg, 6.50 mmol). The mixture was flushed with argon, then benzonitrile (45 mg, 0.43 mmol) in DMA (1 mL), chlorotrimethylsilane (47 mg, 0.43 mmol) in DMA (1 mL) were added and stirred at RT for 1 h and then diluted with water (100 mL). The mixture was extracted with EtOAc (3 x 200 mL), the combined organic layer was dried over anhydr. Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with EtOAc/petroleum ether (0~30%) to afford the title compound.

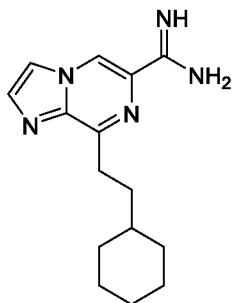
Step C- 8-[(4-methylcyclohexyl)methyl]imidazo[1,2-*a*]pyrazine-6-carbonitrile: Into a flask under an inert atmosphere of N₂, were placed intermediate from **Step B** (200 mg, 0.65 mmol), dicyanozinc (45.7 mg, 0.39 mmol), Pd₂dba₃-chloroform adduct (30 mg, 0.032 mmol), dppf (36 mg, 0.065 mmol), zinc (21 mg, 0.32 mmol) in DMF (1 mL), and the resulting mixture was stirred at 120 °C for 2 h then cooled to RT and diluted with water (200 mL). The mixture was extracted with EtOAc (3 x 200 mL), combined organic layer was dried over anhydr. Na₂SO₄, filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by column chromatography eluting with EtOAc/petroleum ether (0~40%) to afford the title compound.

Step D- 8-[(4-methylcyclohexyl)methyl]imidazo[1,2-*a*]pyrazine-6-carboximidamide: Into a flask under an inert atmosphere of N₂, were placed intermediate from **Step C** (150 mg, 0.59 mmol) in MeOH (3 mL) and NaOMe (64 mg, 1.18 mmol). The reaction mixture was stirred at RT for 2 h, then NH₄Cl (95 mg, 1.77 mmol) was added and the mixture was stirred at 70 °C for 3 h. Upon completion, the solution was concentrated *in vacuo* to dryness. The residue was poured into water (50 mL), and the acidity was adjusted to pH 1-2 with HCl (1 N). The resulting solution was extracted with diethyl ether (2 x 50 mL) and the basicity of the aqueous phase was adjusted to pH 11-12 with sat. aq. NaOH. The resulting solution was

extracted with EtOAc (3 x 100 mL) and the combined organic layer was dried over anhydr. Na₂SO₄, filtered and concentrated *in vacuo* to afford the title compound, **I-A31**. MS: 272 (M + 1). ¹H NMR (300 MHz, CDCl₃) δ 9.05 (s, 1H), 7.78 (d, *J* = 1.2 Hz, 1H), 7.72 (d, *J* = 1.2 Hz, 1H), 5.60-4.60 (br, 3H), 3.22 (d, *J* = 7.5 Hz, 1.5 H), 3.12 (d, *J* = 7.2 Hz, 0.5 H), 2.40-2.27 (m, 1H), 1.73-1.08 (m, 9H), 0.93 (d, *J* = 6.9 Hz, 3H).

INTERMEDIATE A32

8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazine-6-carboximidamide



Step A- 6-bromo-8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazine: Into a flask under an inert atmosphere of N₂, were placed magnesium (0.4 g, 16.25 mmol) and iodine (0.02 g, 0.072 mmol) in THF (5 mL), then (2-bromoethyl)cyclohexane (2.1 g, 10.83 mmol) in THF (10 mL) was added dropwise at 80 °C and the reaction was stirred for 1.5 h, then cooled to RT.

Into another flask under an inert atmosphere of N₂, was placed zinc (II) bromide (2.4 g, 10.83 mmol) in THF (35 mL), followed by the dropwise addition of the Grignard reagent (prepared above) at 0 °C. The mixture was stirred at RT for 1 h, then bis(triphenylphosphine)palladium chloride (0.5 g, 0.72 mmol) and 6,8-dibromoimidazo[1,2-*a*]pyrazine (2 g, 7.22 mmol) were added and stirred at RT for 1.5 h. The reaction was quenched by the addition of sat. aq.

NH₄Cl (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over anhydr. Na₂SO₄, filtered, concentrated to dryness *in vacuo*, and the residue purified by column chromatography with EtOAc/petroleum ether (10-45%) to afford the title compound.

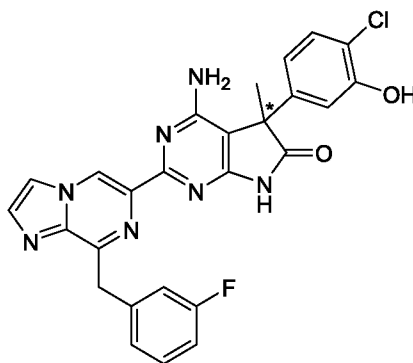
Step B- 8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazine-6-carbonitrile: Into a flask under an inert atmosphere of N₂, were placed intermediate from **Step A** (1 g, 3.24 mmol), dicyanozinc (0.5 g, 4.22 mmol), dppf (0.4 g, 0.649 mmol), Pd₂(dba)₃ (0.3 g, 0.32 mmol), and zinc (0.1 g, 1.62 mmol) in DMF (20 mL). The resulting mixture was stirred at 120 °C for 1 h then cooled, quenched by the addition of water (30 mL) and EtOAc (100 mL), and filtered through a pad of CELITE. The filtrate was extracted with EtOAc (3 x 20 mL) and the combined organic layer dried over anhydr. Na₂SO₄, filtered and concentrated *in vacuo* to dryness. The residue

was purified by column chromatography with EtOAc/petroleum ether (1/1) to afford the title compound.

Step C- 8-(2-cyclohexylethyl)imidazo[1,2-*a*]pyrazine-6-carboximidamide: Into a flask under an inert atmosphere of N₂, was placed sodium (41 mg, 1.77 mmol) in MeOH (10 mL) and the resulting mixture was stirred at RT for 1 h until the sodium bits disappeared. The intermediate from **Step B** (300 mg, 1.18 mmol) was added to the mixture and it was stirred at RT for 1 h, then acetic acid (106 mg, 1.77 mmol) and NH₄Cl (126 mg, 2.36 mmol) were added and the mixture was stirred at 75 °C for 2 h. It was concentrated to dryness *in vacuo*, diluted with water (20 mL), washed with ether (20 mL), and the basicity of the aqueous phase was adjusted to pH 11 with NaOH (1 N) and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over anhydr. Na₂SO₄, filtered and the filtrate concentrated *in vacuo* to afford the title compound, **I-A32**. MS: 272 (M + 1). ¹H NMR (400 MHz, CD₃OD) δ 9.01 (s, 1H), 8.10 (d, *J* = 1.2 Hz, 1H), 7.83 (d, *J* = 0.8 Hz, 1H), 3.32-3.26 (m, 2H), 1.91-1.68 (m, 7H), 1.45-1.38 (m, 1H), 1.37-1.20 (m, 3H), 1.08-0.99 (m, 2H).

EXAMPLE 1-A

4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one

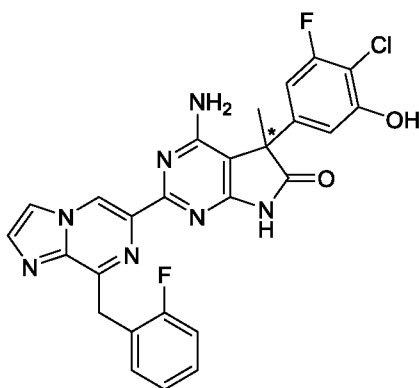


Step A- 4-Amino-5-(4-chloro-3-methoxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one: Into a flask were placed amidine **I-A4** (50 mg, 0.19 mmol), chiral malononitrile **I-12A** (63 mg, 0.20 mmol), *tert*-BuOH (1 mL) and potassium bicarbonate (56 mg, 0.56 mmol). The resulting mixture was stirred at 80 °C for 16 h, then concentrated to dryness *in vacuo*, and the residue was purified by column chromatography eluting with DCM/MeOH (10/1) to afford the title compound.

Step B- 4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one: Into a flask under an inert atmosphere of N₂, was placed intermediate from **Step A** (60 mg, 0.11 mmol) in DCM (1 mL), followed by a dropwise addition of BBr₃ (1.1 mL, 0.57 mmol, 0.5 M in DCM) at 0 °C. The resulting mixture was stirred at RT for 1 h, then quenched with sat. aq. NaHCO₃ (10 mL), extracted with EtOAc (3 x 20 mL) and the combined organic layer was dried over anhydr. Na₂SO₄, filtered and concentrated to dryness *in vacuo*. The residue was purified by column chromatography eluting with hexanes/(3:1) (EtOAc:EtOH) 0-70% to afford the title compound, **1-A**. MS: 516 (M + 1). ¹H NMR (DMSO-*d*₆, 300 MHz): δ 11.19 (br s, 1H), 10.11 (s, 1H), 9.25 (s, 1H), 8.33 (d, *J* = 0.9 Hz, 1H), 7.85 (d, *J* = 0.9 Hz, 1H), 7.36-7.21 (m, 4H), 7.06-7.00 (m, 1H), 6.86 (d, *J* = 2.1 Hz, 1H), 6.75 (dd, *J* = 8.1 Hz, 1.8 Hz, 1H), 6.56 (br s, 2H), 4.54 (s, 2H), 1.75 (s, 3H).

EXAMPLE 2-B

4-Amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one

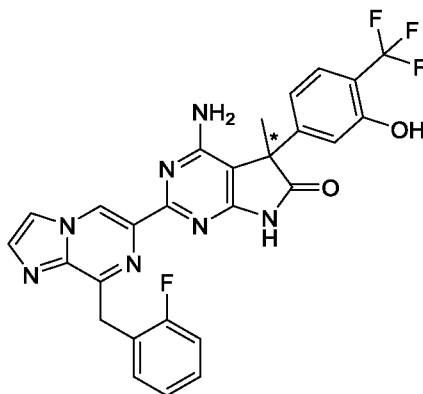


Step A- 4-Amino-5-(4-chloro-3-fluoro-5-methoxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one: Into a flask were placed amidine **I-A3** (70 mg, 0.26 mmol), chiral malononitrile **I-7B** (84 mg, 0.26 mmol), potassium bicarbonate (78 mg, 0.78 mmol) and *tert*-BuOH (5 mL). The resulting mixture was stirred at 80 °C for 16 h, then cooled to RT, quenched by the addition of brine (20 mL), and extracted with EtOAc (3 x 60 mL). The combined organic layer was dried over anhydr. Na₂SO₄, filtered, concentrated to dryness *in vacuo* and the residue was purified by column chromatography eluting with MeOH/DCM (0-2%) to afford the title compound.

Step B- 4-Amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one: Into a flask under an inert atmosphere of N₂, was placed intermediate from **Step A** (70 mg, 0.13 mmol) in DCM (10 ml), followed by a dropwise addition of BBr₃ (1 mL, 10.6 mmol, 1 M in DCM) at 0 °C. The resulting mixture was stirred at RT for 6 h, then poured into a water/ice (50 mL) and the basicity of the solution was adjusted to pH8 with NaHCO₃. The aqueous was extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over anhydr. Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with MeOH/DCM (1%-3%) to afford the title compound, **2-B**. MS: 534 (M + 1). ¹H NMR (300 MHz, CD₃OD) δ 9.40 (s, 1H), 8.11 (d, *J* = 0.9 Hz, 1H), 7.78 (d, *J* = 0.9 Hz, 1H), 7.22-7.15 (m, 2H), 7.08-6.95 (m, 2H), 6.74 (dd, *J* = 2.1, 10.2 Hz, 1H), 6.65 (dd, *J* = 1.5, 1.8 Hz, 1H), 4.66 (s, 2H), 1.79 (s, 3H).

EXAMPLE 3-B

4-Amino-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-[3-hydroxy-4-(trifluoromethyl)phenyl]-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one



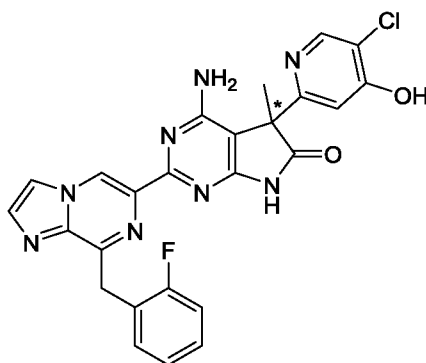
Step A- 4-Amino-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-methoxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one: Into a flask were placed amidine **I-A3** (80 mg, 0.30 mmol), chiral malononitrile **I-9B** (101 mg, 0.30 mmol), potassium bicarbonate (60 mg, 0.60 mmol) and *tert*-BuOH (10 mL). The resulting mixture was stirred at 70 °C for 20 h then concentrated to dryness *in vacuo*, and the residue was purified by column chromatography eluting with MeOH/DCM (1%-7%) to afford the title compound.

Step B- 4-Amino-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one: Into a flask under an inert atmosphere of N₂, was placed intermediate from **Step A** (65 mg, 0.12 mmol) in DCM (7 mL), followed by a dropwise addition of BBr₃ (0.7 mL, 0.12

mmol) at 0 °C. The resulting mixture was stirred for at RT 1 h, then poured into a water/ice (50 mL), and the acidity was adjusted to pH7-8 with solid NaHCO₃. The aqueous was extracted with EtOAc (3 x 50 mL) and the combined organic layer was washed with brine (2 x 50 mL), dried over anhydr. Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography eluting with MeOH/DCM (1%-7%) to afford the title compound, **3-B**. MS: 550 (M + 1). ¹H NMR (CD₃OD, 300 MHz): δ 9.39 (s, 1H), 8.11 (s, 1H), 7.77 (d, *J* = 0.9 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.22-7.15 (m, 2H), 7.07-6.90 (m, 4H), 4.55 (s, 2H), 1.84 (s, 3H).

EXAMPLE 4-B

4-Amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one



Step A- 4-Amino-5-(5-chloro-4-methoxypyridin-2-yl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one: Into a flask were placed amidine **I-A3** (95 mg, 0.35 mmol), chiral malononitrile **I-5B** (90 mg, 0.29 mmol), *tert*-BuOH (6 mL) and potassium bicarbonate (35 mg, 0.35 mmol). The resulting mixture was stirred at 75 °C for 16 h, then concentrated *in vacuo* to dryness and the residue was purified by column chromatography eluting with DCM/MeOH (10/1) to afford the title compound.

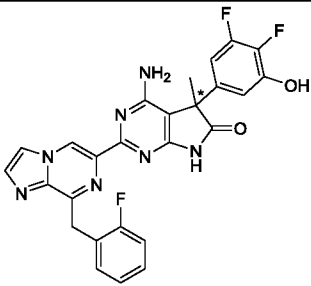
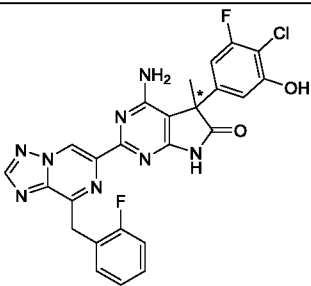
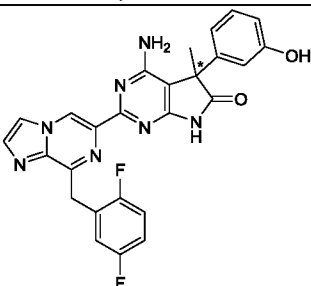
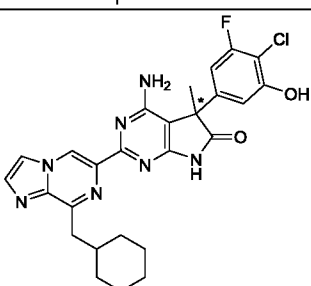
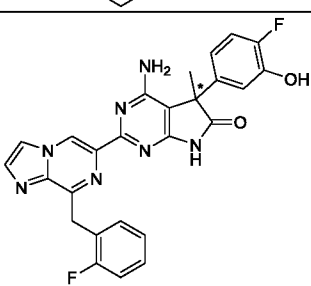
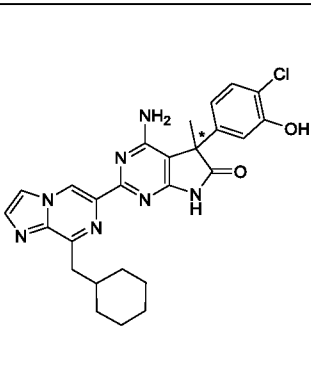
Step B- 4-Amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one: Into a flask were placed intermediate from **Step A** (80 mg, 0.15 mmol) and hydrobromic acid (40%, 8 mL). The resulting mixture was stirred at 80 °C for 16 h then quenched with sat. aq. NaHCO₃ (150 mL), extracted with EtOAc (3 x 100 mL) and the combined organic layer was dried over anhydr. Na₂SO₄, filtered and concentrated to dryness *in vacuo*. The crude product was purified by Prep-HPLC eluting with water (0.05% ammonium bicarbonate) and MeCN (10% ~ 23%) to afford the title compound, **5-B**. MS: 517

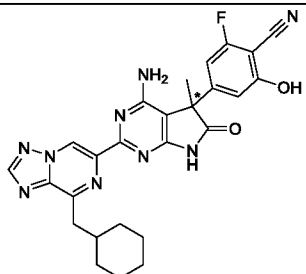
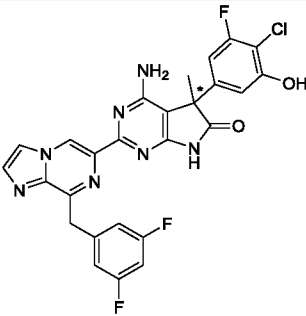
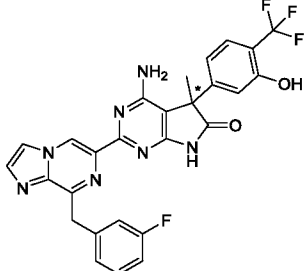
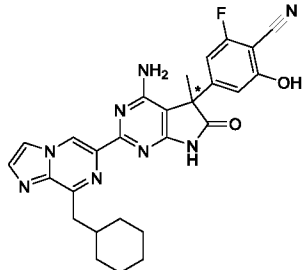
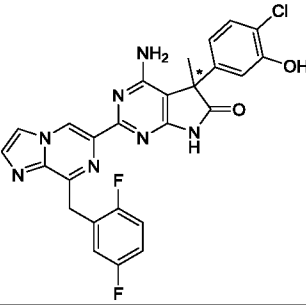
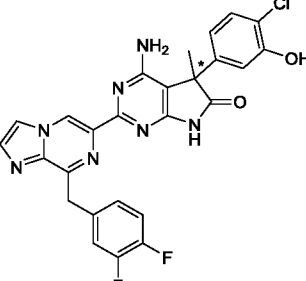
(M + 1). ¹H NMR (CD₃OD, 300 MHz): δ 9.42 (s, 1H), 8.14 (s, 1H), 8.10 (s, 1H), 7.81 (s, 1H), 7.26-7.18 (m, 2H), 7.11-6.99 (m, 2H), 6.64 (s, 1H), 4.69 (s, 2H), 1.87 (s, 3H).

Using essentially the same procedures described in Examples 1 through 4, the following compounds in **Table 5** were prepared. The deprotection step was performed using
5 either BBr₃ or HBr as a deprotecting reagent.

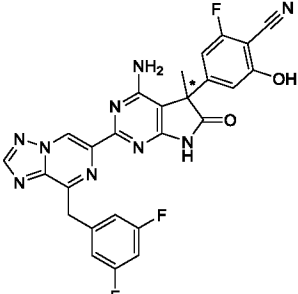
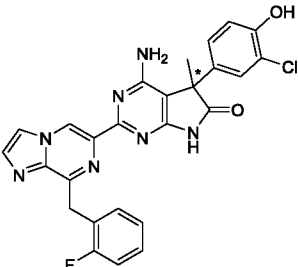
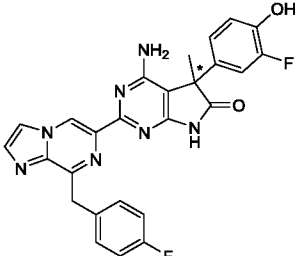
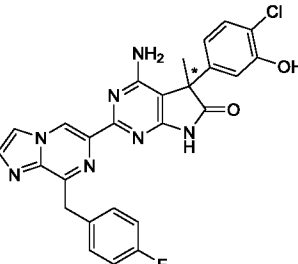
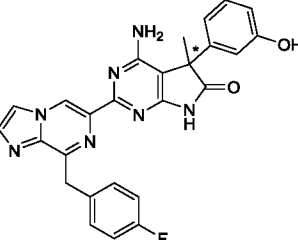
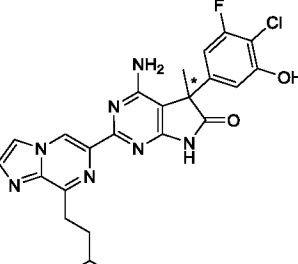
Table 5: Examples 5-B -- 105-B

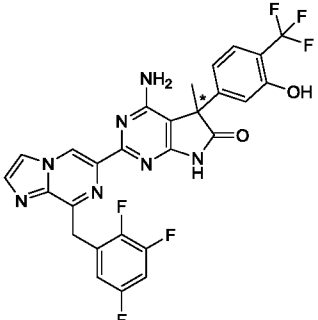
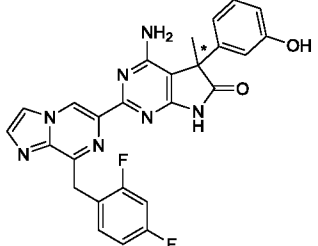
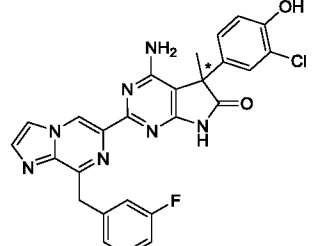
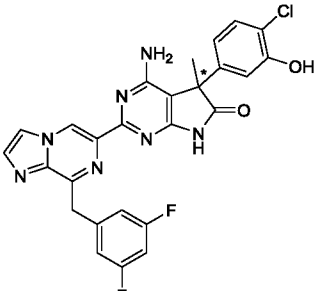
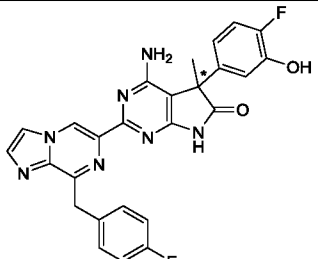
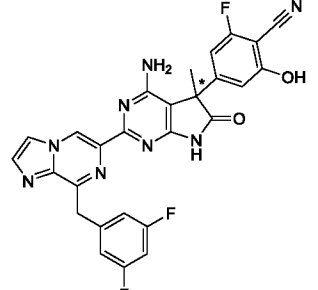
Ex.	Structure	Name	MS (M+1)	Chiral starting material
5-B		4-Amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	534	I-7B
6-B		4-Amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	552	I-7B
7-B		4-Amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-5-methyl-2-{8-[(2,3,5-trifluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	570	I-7B
8-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	516	I-12A

9-B		4-Amino-5-(3,4-difluoro-5-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2- <i>a</i>]pyrazin-6-yl}-5-methyl-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	518	I-8B
10-B		4-Amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]-[1,2,4]triazolo[1,5- <i>a</i>]pyrazin-6-yl}-5-methyl-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	535	I-7B
11-B		4-Amino-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2- <i>a</i>]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	500	I-17B
12-B		4-Amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-(8-(cyclohexylmethyl)imidazo[1,2- <i>a</i>]pyrazin-6-yl)-5-methyl-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	522	I-7B
13-B		4-Amino-5-(4-fluoro-3-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2- <i>a</i>]pyrazin-6-yl}-5-methyl-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	500	I-6B
14-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-(cyclohexylmethyl)imidazo[1,2- <i>a</i>]pyrazin-6-yl)-5-methyl-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	504	I-12A

15-B		4-(4-Amino-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile	514	I-23B
16-B		4-Amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	552	I-7B
17-B		4-Amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	550	I-9B
18-B		4-(4-Amino-2-(8-(cyclohexylmethyl)imidazo[1,2-a]pyrazin-6-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile	513	I-23B
19-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	534	I-12A
20-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3,4-difluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	534	I-12A

21-B		4-Amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	523	I-7B
22-B		4-Amino-2-{8-[(2,4-difluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	518	I-6B
23-B		4-(4-Amino-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile	525	I-23B
24-B		4-Amino-5-(3-fluoro-4-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	500	I-28B
25-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	478	I-12A
26-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]-[1,2,4]triazolo[1,5-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	517	I-12A

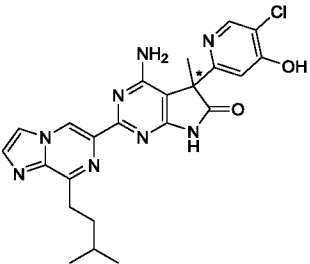
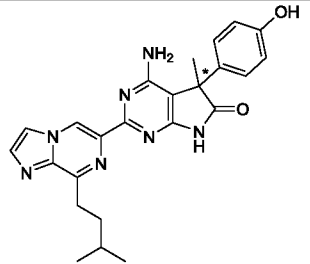
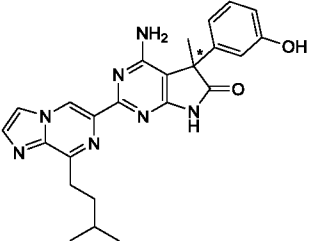
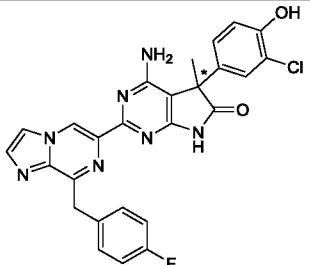
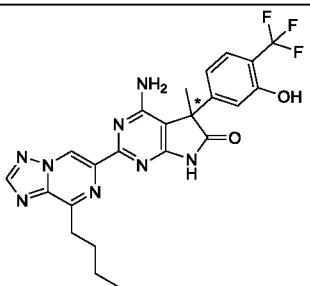
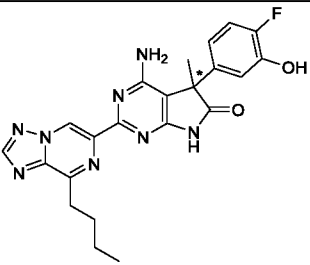
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28-B		4-Amino-5-(3-chloro-4-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2- <i>a</i>]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	516	I-11B
29-B		4-Amino-5-(3-fluoro-4-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2- <i>a</i>]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	501	I-28B
30-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2- <i>a</i>]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	516	I-12A
31-B		4-Amino-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2- <i>a</i>]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	482	I-17B
32-B		4-Amino-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-2-(8-isopentylimidazo[1,2- <i>a</i>]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	496	I-7B

33-B		4-Amino-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-2-((2,3,5-trifluorophenyl)methyl)imidazo[1,2-a]pyrazin-6-yl}-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	586	I-9B
34-B		4-Amino-2-((8-((2,4-difluorophenyl)methyl)imidazo[1,2-a]pyrazin-6-yl)-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	500	I-17B
35-B		4-Amino-5-(3-chloro-4-hydroxyphenyl)-2-((8-((3-fluorophenyl)methyl)imidazo[1,2-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	516	I-11B
36-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-((8-((3,5-difluorophenyl)methyl)imidazo[1,2-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	534	I-12A
37-B		4-Amino-5-(4-fluoro-3-hydroxyphenyl)-2-((8-((4-fluorophenyl)methyl)imidazo[1,2-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	500	I-6B
38-B		4-(4-Amino-2-((8-((3,5-difluorophenyl)methyl)imidazo[1,2-a]pyrazin-6-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile	543	I-23B

39-B		4-Amino-2-(8-butylimidazo[1,2- <i>a</i>]pyrazin-6-yl)-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-5-methyl-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	482	I-7B
40-B		4-Amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2- <i>a</i>]pyrazin-6-yl}-5-methyl-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	535	I-5B
41-B		4-Amino-5-(3-fluoro-4-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]-[1,2,4]triazolo[1,5- <i>a</i>]pyrazin-6-yl}-5-methyl-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	501	I-28B
42-B		4-Amino-2-(8-butyl-1,2,4-triazolo[1,5- <i>a</i>]pyrazin-6-yl)-5-(4-chloro-3-fluoro-5-hydroxyphenyl)-5-methyl-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	483	I-7B
43-B		4-Amino-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2- <i>a</i>]pyrazin-6-yl}-5-(4-hydroxyphenyl)-5-methyl-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	482	I-29B
44-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(4-chlorophenyl)methyl]imidazo[1,2- <i>a</i>]pyrazin-6-yl}-5-methyl-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	532	I-12A

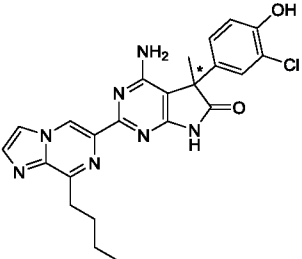
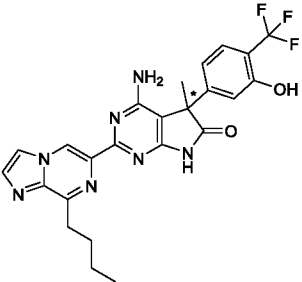
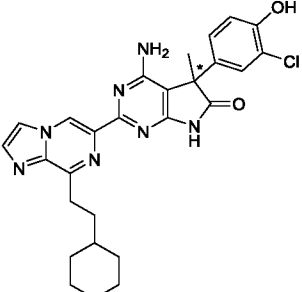
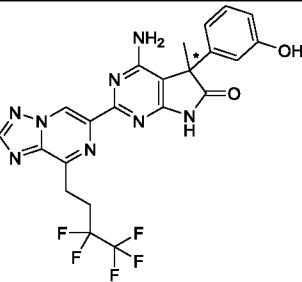
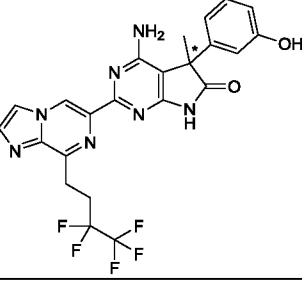
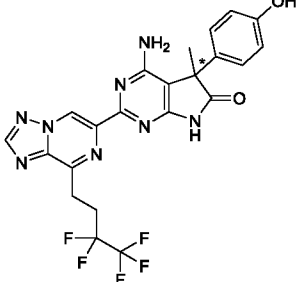
45-A		4-Amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-(4-hydroxy-3-methylphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	496	I-26A
46-B		4-Amino-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	568	I-9B
47-B		4-Amino-5-(4-fluoro-3-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	460	I-6B
48-B		4-Amino-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	500	I-17B
49-A		4-Amino-5-(5-chloro-6-hydroxypyridin-2-yl)-2-(8-(cyclohexylmethyl)imidazo[1,2-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	505	I-16A
50-A		4-Amino-2-(8-butyl-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	465	I-12A

51-B		4-Amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	517	I-5B
52-A		4-Amino-2-(8-butylimidazo[1,2-a]pyrazin-6-yl)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	465	I-12A
53-B		4-Amino-5-(4-chloro-5-hydroxypyridin-2-yl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	517	I-5B
54-B		4-Amino-5-(3-fluoro-4-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	462	I-28B
55-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(4,4,4-trifluorobutyl)imidazo[1,2-a]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	518	I-12A
56-B		4-Amino-2-{8-[(4-chlorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	498	I-17B

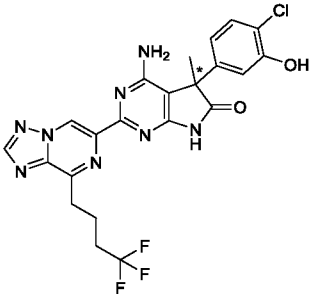
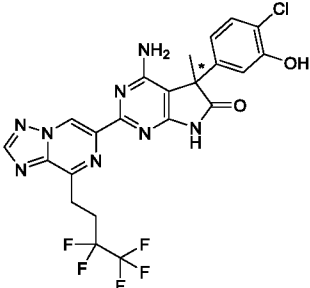
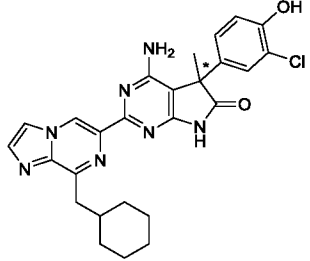
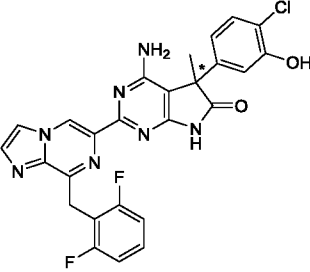
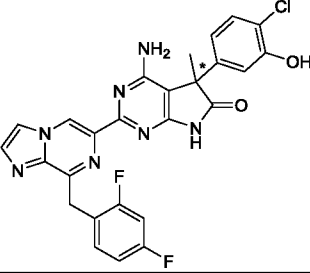
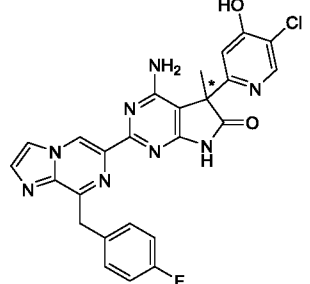
57-B		4-Amino-5-(5-chloro-4-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	479	I-5B
58-B		4-Amino-5-(4-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	444	I-29B
59-B		4-Amino-5-(3-hydroxyphenyl)-2-(8-isopentylimidazo[1,2-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	444	I-17B
60-B		4-Amino-5-(3-chloro-4-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	516	I-11B
61-B		4-Amino-2-(8-butyl-1,2,4-triazolo[1,5-a]pyrazin-6-yl)-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	499	I-9B
62-B		4-Amino-2-(8-butyl-1,2,4-triazolo[1,5-a]pyrazin-6-yl)-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	449	I-6B

63-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-(2-cyclohexylethyl)imidazo[1,2-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	518	I-12A
64-B		4-Amino-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-2-(8-isopentylimidazo[1,2-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	512	I-9B
65-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-a]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	554	I-12A
66-B		4-Amino-5-(3-chloro-4-hydroxyphenyl)-2-{8-[(4-fluorophenyl)methyl]-[1,2,4]triazolo[1,5-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	517	I-11B
67-A		4-Amino-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5-(2,4-dichloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	539	I-19A
68-B		4-Amino-2-(8-butyl-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	431	I-17B

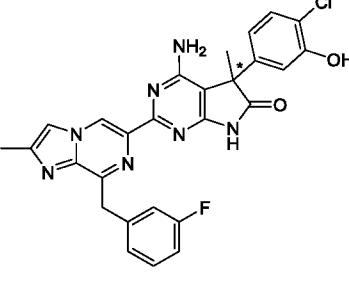
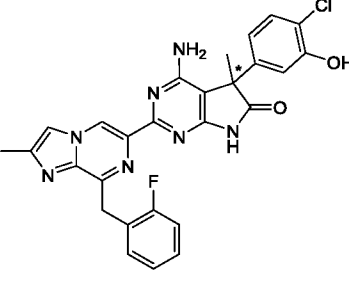
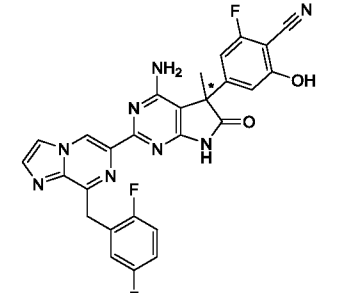
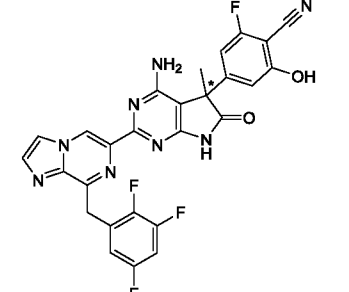
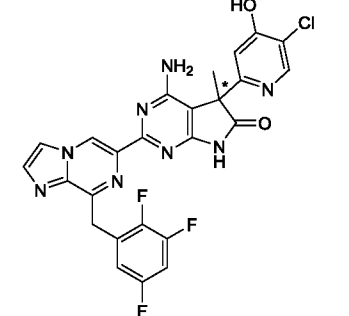
69-A		4-Amino-2-(8-(cyclohexylmethyl)imidazo[1,2-a]pyrazin-6-yl)-5-(2,4-dichloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	538	I-19A
70-B		4-Amino-2-(8-butyl-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5-(4-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	431	I-29B
71-B		4-Amino-2-(8-butyl-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	449	I-28B
72-B		4-Amino-2-(8-butylimidazo[1,2-a]pyrazin-6-yl)-5-(5-chloro-4-hydroxypyridin-2-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	465	I-5B
73-A		4-Amino-5-(3,5-dichloro-4-hydroxypyridin-2-yl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	569 (M - 1)	I-15A
74-B		4-Amino-2-(8-butyl-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5-(3-chloro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	465	I-11B

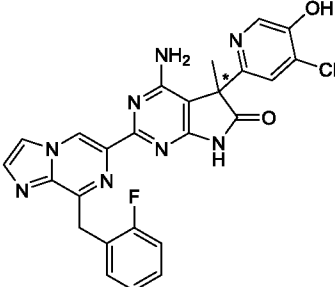
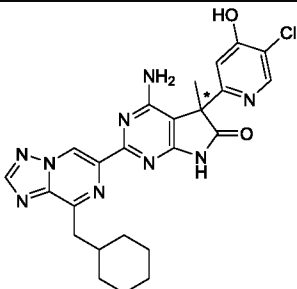
75-B		4-Amino-2-(8-butylimidazo[1,2- <i>a</i>]pyrazin-6-yl)-5-(3-chloro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	464	I-11B
76-B		4-Amino-2-(8-butylimidazo[1,2- <i>a</i>]pyrazin-6-yl)-5-(3-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	498	I-9B
77-B		4-Amino-5-(3-chloro-4-hydroxyphenyl)-2-(8-(2-cyclohexylethyl)imidazo[1,2- <i>a</i>]pyrazin-6-yl)-5-methyl-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	518	I-11B
78-B		4-Amino-5-(3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5- <i>a</i>]pyrazin-6-yl)-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	521	I-17B
79-B		4-Amino-5-(3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2- <i>a</i>]pyrazin-6-yl)-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	520	I-17B
80-B		4-Amino-5-(4-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5- <i>a</i>]pyrazin-6-yl)-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	521	I-29B

81-B		4-Amino-5-(4-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-a]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	520	I-29B
82-B		4-Amino-2-(8-(cyclohexylmethyl)imidazo[1,2-a]pyrazin-6-yl)-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	470	I-17B
83-B		4-Amino-2-(8-(2-cyclohexylethyl)imidazo[1,2-a]pyrazin-6-yl)-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	484	I-17B
84-B		4-Amino-2-(8-(2-cyclohexylethyl)imidazo[1,2-a]pyrazin-6-yl)-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	502	I-28B
85-B		4-Amino-2-(8-(2-cyclohexylethyl)imidazo[1,2-a]pyrazin-6-yl)-5-(4-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	484	I-29B
86-B		4-Amino-2-(8-(2-cyclohexylethyl)imidazo[1,2-a]pyrazin-6-yl)-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	502	I-6B

87-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(4,4,4-trifluorobutyl)-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	519	I-12A
88-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	555	I-12A
89-B		4-Amino-5-(3-chloro-4-hydroxyphenyl)-2-(8-(cyclohexylmethyl)imidazo[1,2-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	504	I-11B
90-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2,6-difluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	534	I-12A
91-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2,4-difluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	534	I-12A
92-B		4-Amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(4-fluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	517	I-5B

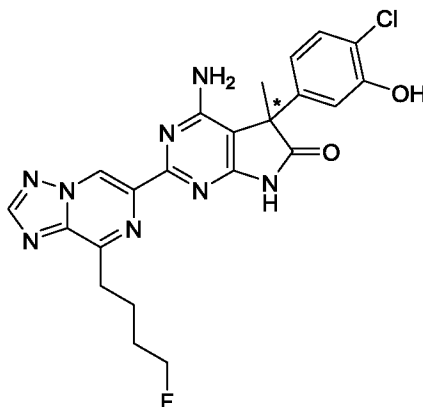
93-B		4-Amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-(8-(cyclohexylmethyl)imidazo[1,2-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	505	I-5B
94-B		4-Amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	535	I-5B
95-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-[(4,4-difluorocyclohexyl)methyl]imidazo[1,2-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	540	I-12A
96-B		4-Amino-5-(3-chloro-4-fluoro-2-hydroxyphenyl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	552	I-20B
97-B		4-Amino-2-(8-(cyclohexylmethyl)imidazo[1,2-a]pyrazin-6-yl)-5-(3-fluoro-5-hydroxy-4-(trifluoromethyl)phenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	556	I-24B
98-B		4-Amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-{8-[(2,6-difluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	535	I-5B

99-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]-2-methylimidazo[1,2- <i>a</i>]pyrazin-6-yl}-5-methyl-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	530	I-12A
100-A		4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-{8-[(2-fluorophenyl)methyl]-2-methylimidazo[1,2- <i>a</i>]pyrazin-6-yl}-5-methyl-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	530	I-12A
101-B		4-(4-Amino-2-{8-[(2,5-difluorophenyl)methyl]imidazo[1,2- <i>a</i>]pyrazin-6-yl}-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile	543	I-23B
102-B		4-(4-Amino-5-methyl-6-oxo-2-{8-[(2,3,5-trifluorophenyl)methyl]imidazo[1,2- <i>a</i>]pyrazin-6-yl}-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)-2-fluoro-6-hydroxybenzonitrile	561	I-23B
103-B		4-Amino-5-(5-chloro-4-hydroxypyridin-2-yl)-5-methyl-2-{8-[(2,3,5-trifluorophenyl)methyl]imidazo[1,2- <i>a</i>]pyrazin-6-yl}-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	553	I-5B

104-B		4-Amino-5-(4-chloro-5-hydroxypyridin-2-yl)-2-{8-[(2-fluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	517	I-10B
105-B		4-Amino-5-(5-chloro-4-hydroxypyridin-2-yl)-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	506	I-5B

EXAMPLE 106-A

4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-(4-fluorobutyl)-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one



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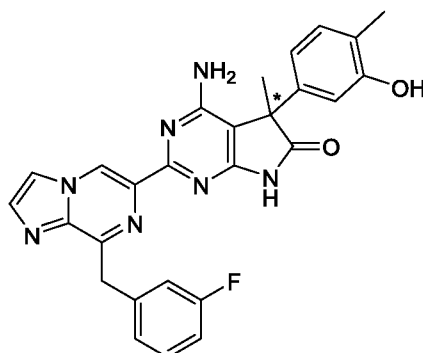
4-Amino-5-(4-chloro-3-hydroxyphenyl)-2-(8-(4-fluorobutyl)-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one: Into a flask were placed amidine **I-A19** (100 mg, 0.35 mmol), chiral Br-Lactam **I-25A** (114 mg, 0.35 mmol), 1,4-dioxane (10 mL) and Et₃N (0.24 mL, 1.74 mmol). The resulting mixture was stirred at 75 °C for 16 h, then quenched with water (100 mL), extracted with EtOAc (3 x 50 mL) and the combined organic layer was dried over anhydr. Na₂SO₄, filtered and concentrated to dryness *in vacuo*. The crude product was washed with MeOH (3 x 2 mL) to afford the title compound, **106-A**. MS: 483 (M + 1). ¹H NMR (DMSO-*d*₆, 300 MHz): δ 11.25 (br s, 1H), 10.12 (s, 1H), 9.39 (s, 1H), 8.77 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 1.8 Hz, 1H), 6.75 (dd, *J* = 1.8 Hz, 8.1 Hz, 1H), 6.64 (br s, 2H), 4.59 (t, *J* = 6.0 Hz, 1H), 4.43 (t, *J* = 6.0 Hz, 1H), 3.27 (t, *J* = 7.8 Hz, 2H), 2.03-1.93 (m, 2H), 1.87-1.75 (m, 5H).

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EXAMPLE 107-B

4-Amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxy-4-methylphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one



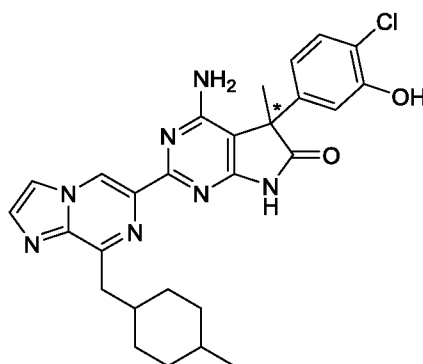
5 **Step A- 4-Amino-5-(3-((tert-butyldimethylsilyl)oxy)-4-methylphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5*H*-pyrrolo[2,3-*d*]pyrimidin-6(7*H*)-one:** Into a flask were placed amidine **I-A4** (120 mg, 0.45 mmol), rac. malononitrile **I-27** (172 mg, 0.45 mmol), potassium bicarbonate (223 mg, 2.23 mmol) and *tert*-BuOH (5 mL). The resulting mixture was stirred at 75 °C for 16 h, then concentrated *in vacuo* and the residue was purified by column chromatography eluting with DCM/MeOH (10/1) to afford the title compound. The racemic material was resolved using chiral-prep-HPLC Column (Phenomenex Lux 5u Cellulose-4, AXIA) to afford isomers **A** (faster eluting) and **B** (slower eluting) of the title compound.

15 **Step B- 4-Amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxy-4-methylphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one:** Into a flask, were placed enantiomer **B** from **Step A** (65 mg, 0.11 mmol), THF (3 mL) and TBAF (37 mg, 0.12 mmol). The resulting solution was stirred at RT for 15 min, then quenched with water (10 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (15 mL), dried over anhydr. Na₂SO₄, filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by column chromatography eluting with DCM/MeOH (10/1) to afford the title compound, **107-B**. MS: 496 (M + 1). ¹H NMR (400 MHz, CD₃OD) δ 9.40 (s, 1H), 8.13 (d, *J* = 0.8 Hz, 1H), 7.84 (d, *J* = 1.2 Hz, 1H), 7.32-7.22 (m, 3H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.92 (dd, *J* = 9.2, 8.8 Hz, 1H), 6.77-6.71 (m, 2H), 4.63 (s, 2H), 2.15 (s, 3H), 1.83 (s, 3H).

25

EXAMPLE 108-AB

4-Amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-{8-[(4-methylcyclohexyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one



Step A- 4-Amino-5-(4-chloro-3-methoxyphenyl)-5-methyl-2-{8-[(4-methylcyclohexyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one: Into a flask were placed amidine **I-A31** (150 mg, 0.55 mmol), chiral

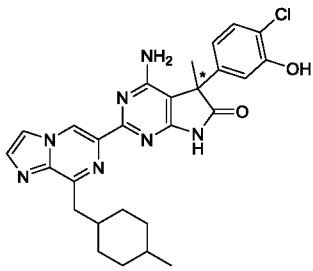
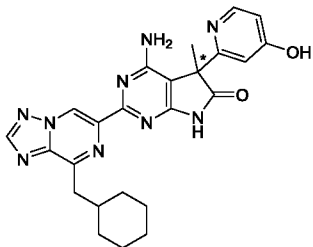
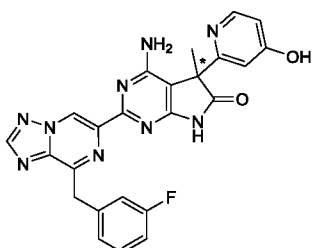
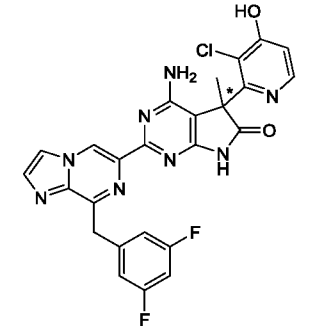
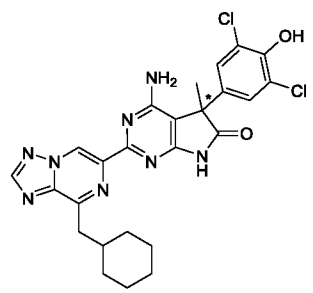
malononitrile **I-12A** (170 mg, 0.55 mmol), potassium bicarbonate (111 mg, 1.11 mmol) and *tert*-BuOH (2 mL). The mixture was stirred at 70 °C for 16 h, then cooled to RT and concentrated *in vacuo*. The residue was purified by column chromatography eluting with MeOH/DCM (0~5%) to afford a cis/trans mixture of the title compound. The cis/trans diastereomers were resolved using Chiral-Prep-HPLC SFC Column (**CHIRALPAK IC**) to afford isomers **A** (faster eluting) and **B** (slower eluting) of the title compound.

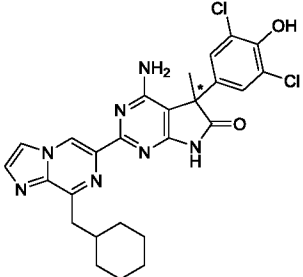
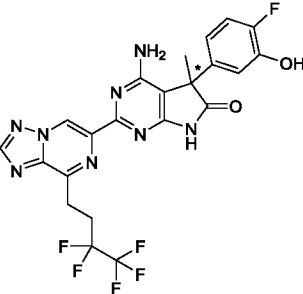
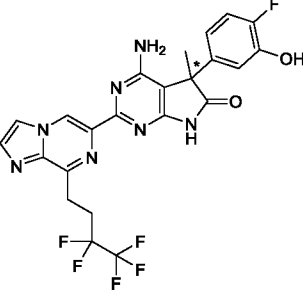
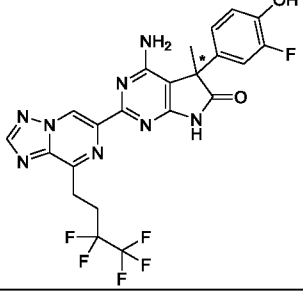
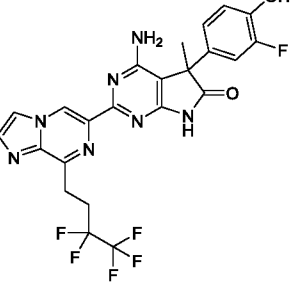
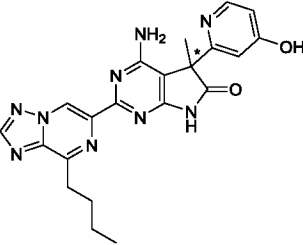
Step B- 4-Amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-{8-[(4-methylcyclohexyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one: Into a flask was placed enantiomer **B** (slower eluting) from **Step A**, (50 mg, 0.094 mmol) in DCM (2 mL), followed by a dropwise addition of BBr₃ (235 mg, 0.940 mmol) at 0 °C. The resulting mixture was stirred at RT for 1 h then poured into ice-water (10 mL) and the basicity of the solution was adjusted to pH8 with sat. aq. NaHCO₃. It was extracted with EtOAc (3 x 100 mL) and the combined organic layer was dried over anhydr. Na₂SO₄, filtered and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography eluting with MeOH/DCM (0~5%) to afford the title compound, **108-AB**.

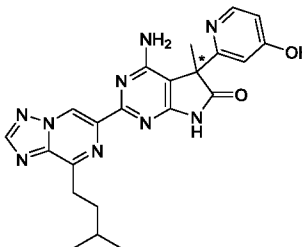
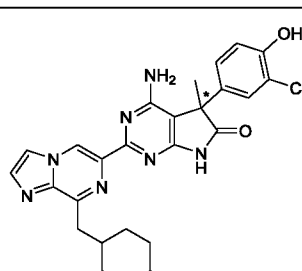
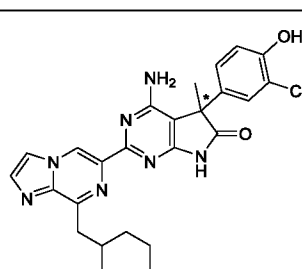
MS: 518 (M + 1). ¹H NMR (300 MHz, CD₃OD) δ 9.31 (s, 1H), 8.07 (s, 1H), 7.78 (s, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 2.1 Hz, 1H), 6.80 (dd, *J* = 2.1, 8.4 Hz, 1H), 3.14 (d, *J* = 7.2 Hz, 2H), 2.10-1.95 (m, 1H), 1.81 (s, 3H), 1.67-1.64 (m, 4H), 1.46-1.12 (m, 3H), 0.98-0.82 (m, 5H).

Using essentially the same procedures described in **Example 107-B** and **108-AB**, the following compounds in **Table 6** were prepared. The deprotection step was performed using either BBr₃, HBr or TBAF as a deprotecting reagent.

Table 6: Examples 108-AA – 120-BB

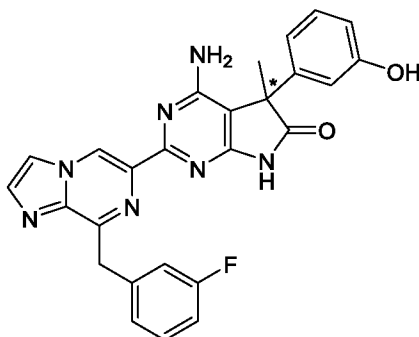
Ex.	Structure	Name	MS (M+1)	Int. SM/Chiral Resolution Column
108-AA		4-Amino-5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-{8-[(4-methylcyclohexyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	518	I-12A / CHIRALPAK IC
109-A		4-Amino-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5-(4-hydroxypyridin-2-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	472	I-13 / CHIRALPAK IF
110-B		4-Amino-2-{8-[(3-fluorophenyl)methyl]-[1,2,4]triazolo[1,5-a]pyrazin-6-yl}-5-(4-hydroxypyridin-2-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	484	I-13 / CHIRALPAK IC
111-B		4-Amino-5-(3-chloro-4-hydroxypyridin-2-yl)-2-{8-[(3,5-difluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	535	I-14 / CHIRAL ART Cellulose-SB
112-B		4-Amino-2-(8-(cyclohexylmethyl)-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5-(3,5-dichloro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	539	I-18 / Phenomenex Lux 5u Cellulose-4, AXIA

113-A		4-Amino-2-(8-(cyclohexylmethyl)imidazo[1,2-a]pyrazin-6-yl)-5-(3,5-dichloro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	538	I-18 / CHIRALPAK AD-H
114-B		4-Amino-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	539	Rac. I-6 / CHIRALPAK IA
115-B		4-Amino-5-(4-fluoro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-a]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	538	Rac. I-6 / (R,R)WHELK-01 5/100 Kromasil
116-B		4-Amino-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	539	Rac. I-28 / CHIRALPAK IB
117-B		4-Amino-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-a]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	538	Rac. I-28 / CHIRALPAK IB
118-B		4-Amino-2-(8-butyl-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5-(4-hydroxypyridin-2-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	432	I-13 / CHIRALPAK IC

119-B		4-Amino-5-(4-hydroxypyridin-2-yl)-2-(8-isopentyl-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	446	I-13 / CHIRALPAK IC
120-BA		4-Amino-5-(3-chloro-4-hydroxyphenyl)-5-methyl-2-{8-[(4-methylcyclohexyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	518	I-11B / CHIRAL ART Cellulose-SB
120-BB		4-Amino-5-(3-chloro-4-hydroxyphenyl)-5-methyl-2-{8-[(4-methylcyclohexyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	518	I-11B / CHIRAL ART Cellulose-SB

EXAMPLE 121-B

4-Amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one



5

Step A- 4-Amino-5-(3-methoxyphenyl)-5-methyl-2-(8-(methylthio)imidazo[1,2-a]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one:

Into a flask under an inert atmosphere of N₂, were placed *t*-BuOH (39 mL), chiral malononitrile **I-17B** (2.36 g, 8.65 mmol), amidine **I-A21** (1.63 g, 7.86 mmol) and potassium bicarbonate (2.36 g, 23.6 mmol).

10 The mixture was stirred at 80 °C for 16 h, then cooled to RT, quenched with water (50 mL), and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydr. Na₂SO₄, the solid was filtered and the filtrate concentrated *in vacuo* to dryness. The crude

was triturated with EtOAc and hexanes, and dried to afford the title compound.

Step B- 4-Amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-methoxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one:

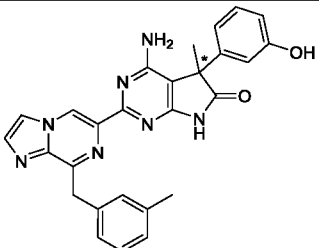
Into a flask under an inert atmosphere of N₂ were placed intermediate from **Step A** (500 mg, 1.15 mmol), Xantphos generation II precatalyst (91 mg, 0.12 mmol), and (3-fluorobenzyl)zinc(II) chloride (11.5 mL, 5.77 mmol, 0.5 M in THF), and the mixture was stirred at 70 °C for 48 h. It was cooled, diluted with EtOAc (100 mL), and passed through a pad of CELITE. The filtrate was dried over anhydr. Na₂SO₄, and concentrated *in vacuo* to dryness. The crude residue was purified by column chromatography eluting with DCM/MeOH 0-3% to afford the title compound.

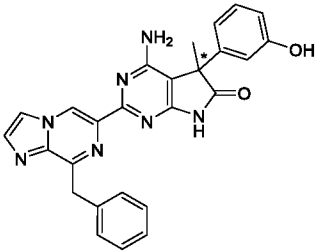
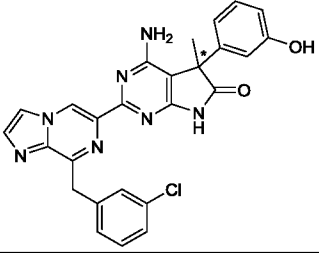
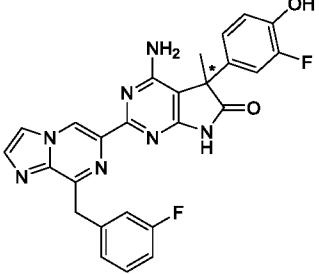
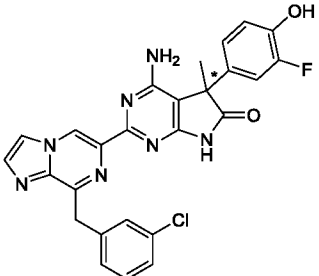
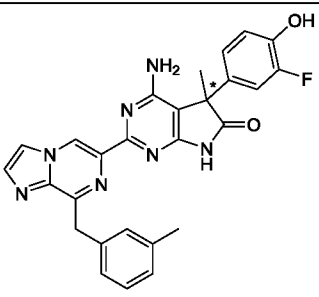
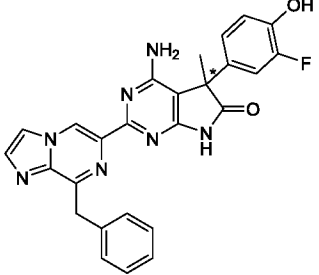
Step C- 4-Amino-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one:

Into a flask under an inert atmosphere of N₂ was placed intermediate from **Step B** (140 mg, 0.28 mmol) in DCM (1.4 mL), followed by a dropwise addition of BBr₃ (1.4 mL, 1.41 mmol, 1 M in DCM) at 0 °C. The reaction was stirred at RT for 48 h, then quenched with sat. aq. Na₂CO₃ (20 mL), and diluted with EtOAc (50 mL). The aqueous was extracted with EtOAc (3 x 20 mL), the combined organic layer was dried over anhydr. Na₂SO₄ and the filtrate concentrated *in vacuo* to dryness. The residue was purified by RP-HPLC eluting with MeCN/water (0.05 % v/v TFA) 0-40%. The resultant residue was free-based with sat. aq. NaHCO₃ to afford the title compound, **121-B**. MS: 482 (M + 1). ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.15 (1 H, s), 9.35 (1 H, s), 9.24 (1 H, s), 8.31 (1 H, s), 7.83 (1 H, s), 7.30 (1 H, dd, *J* = 8.0, 8.0 Hz), 7.21 (2 H, d, *J* = 8.0 Hz), 7.14-7.09 (1 H, m), 7.03-6.99 (1 H, m), 6.70 (1 H, d, *J* = 8.0 Hz), 6.66-6.64 (2 H, m), 4.52 (2 H, s), 1.73 (3 H, s).

Using essentially the same procedures described in **Example 121-B**, the following compounds in **Table 7** were prepared using commercially available organozinc reagents.

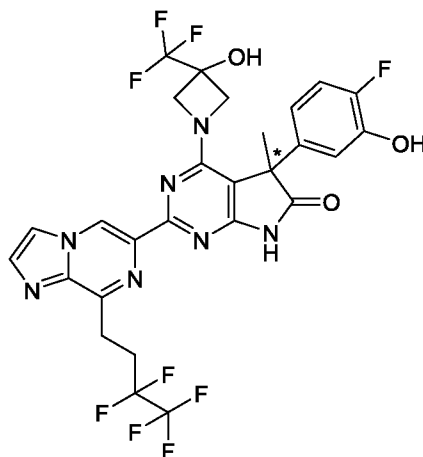
Table 7: Examples 122-B – 128-B

Ex.	Structure	Name	MS (M+1)	Chiral starting material
122-B		4-Amino-5-(3-hydroxyphenyl)-5-methyl-2-{8-[(3-methylphenyl)methyl]imidazo[1,2- <i>a</i>]pyrazin-6-yl}-5,7-dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-	478	I-17B

		6-one		
123-B		4-Amino-2-(8-benzylimidazo[1,2-a]pyrazin-6-yl)-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	464	I-17B
124-B		4-Amino-2-{8-[(3-chlorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	498	I-17B
125-B		4-Amino-5-(3-fluoro-4-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	500	I-28B
126-B		4-Amino-2-{8-[(3-chlorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	516	I-28B
127-B		4-Amino-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-2-{8-[(3-methylphenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	496	I-28B
128-B		4-Amino-2-(8-benzylimidazo[1,2-a]pyrazin-6-yl)-5-(3-fluoro-4-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	482	I-28B

EXAMPLE 129-B

5-(4-fluoro-3-hydroxyphenyl)-4-(3-hydroxy-3-(trifluoromethyl)azetidin-1-yl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one



5 **Step A- 4-amino-5-(4-fluoro-3-methoxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one:** Into a flask were placed amidine **I-A12** (300 mg, 0.976 mmol), rac. malononitrile **I-6** (312 mg, 1.074 mmol) and potassium bicarbonate (293 mg, 2.93 mmol) in *t*-BuOH (8 ml). The reaction mixture was stirred at 75°C for 16 h, then concentrated *in vacuo* to dryness and
10 the residue was purified by column chromatography with petroleum ether/EtOAc (50%) to afford the title compound.

Step B- 4-chloro-5-(4-fluoro-3-methoxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one: Into a flask under an inert atmosphere of N₂, were placed racemic intermediate from
15 **Step A** (330 mg, 0.60 mmol), and copper(II) chloride (483 mg, 3.59 mmol) in DCE (10 mL), then *tert*-butyl nitrite (370 mg, 3.59 mmol) was added and the mixture was stirred at 65 °C for 4 h. The reaction was cooled to RT, quenched with NH₄Cl/ammonia (9/1, 100 mL) and extracted with EtOAc (3 x 20 mL). Combined organic layer was dried over anhydr. Na₂SO₄, filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by
20 column chromatography eluting with petroleum ether/EtOAc (50-100%) to afford the title compound.

Step C- 5-(4-fluoro-3-methoxyphenyl)-4-(3-hydroxy-3-(trifluoromethyl)azetidin-1-yl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one: Into a flask were placed 3-(trifluoromethyl)azetidin-3-ol hydrochloride (154 mg, 0.87 mmol) in THF (3 mL) and Et₃N (0.13 mL, 0.93 mmol) and the mixture was stirred at RT for 15 min. The solid was filtered out and the filtrate was added

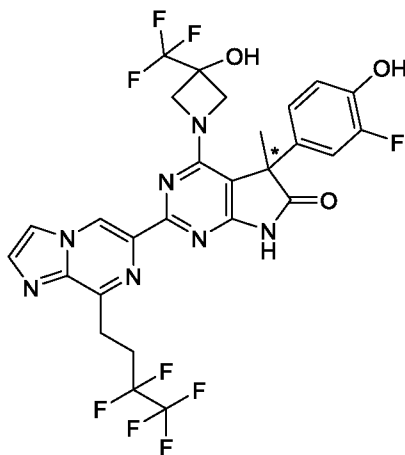
into a 5-mL microwave vial, followed by the addition of the intermediate from **Step B** (165 mg, 0.29 mmol). The mixture was irradiated with microwave radiation at 150 °C for 40 min, then concentrated *in vacuo*. The residue was purified by column chromatography with EtOAc/petroleum ether (50-100%) and then by Prep-HPLC with water (10% ammonium bicarbonate)/MeCN 0-50% to afford the racemic title compound. The racemic material was resolved using Prep-Chiral-HPLC Column (R,R)WHELK-01 5/100 Kromasil to afford isomers **A** (faster eluting) and **B** (slower eluting) of the title compound.

Step D-5-(4-fluoro-3-hydroxyphenyl)-4-(3-hydroxy-3-(trifluoromethyl)azetidin-1-yl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6H-

pyrrolo[2,3-*d*]pyrimidin-6-one: Into a flask under an inert atmosphere of N₂ was placed the slower eluting enantiomer from **Step C** (8 mg, 0.012 mmol) in DCM (2 mL), followed by a dropwise addition of BBr₃ (0.2 mL, 2.12 mmol) at 0 °C. The reaction was stirred at RT for 16 h, then quenched with sat. aq. Na₂CO₃ (20 mL), and extracted with EtOAc (3 x 20 mL), the combined organic layer was dried over anhydr. Na₂SO₄ and the filtrate concentrated *in vacuo* to dryness. The residue was purified by RP HPLC eluting with MeCN/water (0.1% NaHCO₃) 35-75% to afford the title compound, **129-B**. MS: 662 (M + 1). ¹H NMR (300 MHz, CD₃OD): δ 9.45 (s, 1H), 8.18 (d, *J* = 0.9 Hz, 1H), 7.85 (d, *J* = 0.9 Hz, 1H), 7.08 (dd, *J* = 8.7, 10.8 Hz, 1H), 6.84 (dd, *J* = 2.4, 8.1 Hz, 1H), 6.75 (dd, *J* = 4.2, 6.6 Hz, 1H), 4.38 (d, *J* = 10.2 Hz, 1H), 4.12 (d, *J* = 10.2 Hz, 1H), 3.93 (d, *J* = 10.2 Hz, 1H), 3.71-3.60 (m, 3H), 3.08-2.87 (m, 2H), 1.87 (s, 3H).

EXAMPLE 130-A

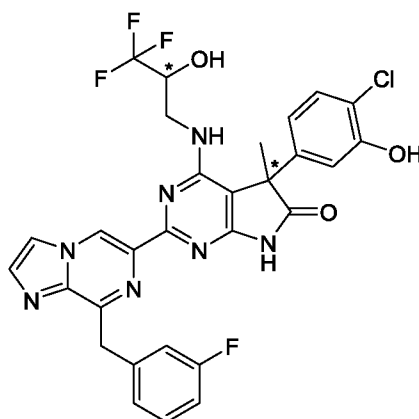
5-(3-fluoro-4-hydroxyphenyl)-4-(3-hydroxy-3-(trifluoromethyl)azetidin-1-yl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)imidazo[1,2-*a*]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one



Example 130-A was prepared following essentially the same procedure as described in **Example 129-B**, using amidine **I-A12** and rac. malononitrile **I-28** as starting materials. The racemic material was resolved at **Step C** using Prep-Chiral-HPLC Column: CHIRALPAK IA. The first eluted enantiomer **A** was carried on to the **Step D** to afford the title compound, **130-A**. MS: 663 ($M + 1$). ^1H NMR (300 MHz, CD_3OD): δ 9.45 (s, 1H), 8.18 (d, $J = 0.9$ Hz, 1H), 7.84 (d, $J = 0.9$ Hz, 1H), 7.02 (dd, $J = 8.7, 10.8$ Hz, 1H), 6.99-6.85 (m, 2H), 4.37 (d, $J = 10.2$ Hz, 1H), 4.11 (d, $J = 10.2$ Hz, 1H), 3.91 (d, $J = 10.2$ Hz, 1H), 3.70-3.60 (m, 3H), 3.01-2.88 (m, 2H), 1.82 (s, 3H).

EXAMPLE 131-AB

5-(4-chloro-3-hydroxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-4-[(3,3,3-trifluoro-2-hydroxypropyl)amino]-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one



Step A- 4-Amino-5-(4-chloro-3-methoxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one: Into a flask were placed amidine **I-A4** (1.3 g, 4.83 mmol), chiral malononitrile **I-12A** (1.5 g, 4.83 mmol), *tert*-BuOH (40 mL) and potassium bicarbonate (0.60 g, 5.79 mmol). The resulting mixture was stirred at 80 °C for 16 h, then concentrated to dryness *in vacuo*, and the residue was purified by column chromatography eluting with DCM/MeOH (10/1) to afford the title compound.

Step B- 4-chloro-5-(4-chloro-3-methoxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one: Into a flask under an inert atmosphere of N_2 , were placed copper(II) chloride (335 mg, 2.49 mmol), intermediate from **Step A**, (330 mg, 0.62 mmol) in DMF (1 mL) and DCE (5 mL), followed by the addition of *tert*-butyl nitrite (449 mg, 4.36 mmol). The mixture was stirred for at 65 °C 1 h, then quenched with NH_4Cl /ammonia (9/1, 100 mL),

extracted with EtOAc (3 x 100 mL), and the combined organic layer was washed with water (2 x 100 mL), dried over anhydr. Na₂SO₄, filtered and concentrated *in vacuo* to dryness. The residue was purified by column chromatography with EtOAc/petroleum ether (0-60%) to afford the title compound.

- 5 **Step C- 5-(4-chloro-3-methoxyphenyl)-2-(8-(3-fluorobenzyl)imidazo[1,2-a]pyrazin-6-yl)-5-methyl-4-[(3,3,3-trifluoro-2-hydroxypropyl)amino]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one:** Into a microwave vial under an inert atmosphere of N₂, were placed intermediate from **Step B** (220 mg, 0.40 mmol), in *N*-methyl-2-pyrrolidinone (3 mL) and THF (3 mL), and 3-amino-1,1,1-trifluoropropan-2-ol (207 mg, 1.60 mmol). The mixture was
10 irradiated with microwave radiation at 180 °C for 3 h, then cooled to RT, quenched with water (100 mL), and extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with water (2 x 100 mL), dried over anhydr. Na₂SO₄, filtered and concentrated *in vacuo* to dryness. The residue was purified by column chromatography with MeOH/DCM (0-5%) to afford the racemic title compound, which was resolved by chiral-prep-HPLC Column
15 Phenomenex Lux 5u Cellulose-4, to afford isomers **A** (faster eluting) and **B** (slower eluting) of the title compound.

- Step D 5-(4-chloro-3-hydroxyphenyl)-2-(8-(3-fluorobenzyl)imidazo[1,2-a]pyrazin-6-yl)-5-methyl-4-[(3,3,3-trifluoro-2-hydroxypropyl)amino]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one:** Into a flask under an inert atmosphere of N₂ was placed the slower
20 eluting enantiomer **B** from **Step C** (70 mg, 0.11 mmol) in DCM (2 mL), followed by a dropwise addition of BBr₃ (137 mg, 0.55 mmol) at 0 °C. The reaction was stirred at RT for 1 h, then quenched with ice-water (10 mL) and the basicity of the solution was adjusted to pH8 with solid NaHCO₃. The resulting solution was extracted with EtOAc (3 x 100 mL), the combined organic layer was dried over anhydr. Na₂SO₄ and the filtrate concentrated *in vacuo*
25 to dryness. The residue was purified by column chromatography with MeOH/DCM (0~5%) to afford the title compound, **131AB**. MS: 628 (M + 1). ¹H NMR (300 MHz, CD₃OD) δ 9.35 (s, 1H), 8.10 (d, *J* = 0.9 Hz, 1H), 7.82 (d, *J* = 0.9 Hz, 1H), 7.38-7.31 (m, 2H), 7.26-7.17 (m, 2H), 6.89-6.83 (m, 2H), 6.77 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.58 (s, 2H), 4.25-4.17 (m, 1H), 3.89 (dd, *J* = 3.3, 14.4 Hz, 1H), 3.65 (dd, *J* = 7.2, 14.4 Hz, 1H), 1.81 (s, 3H).

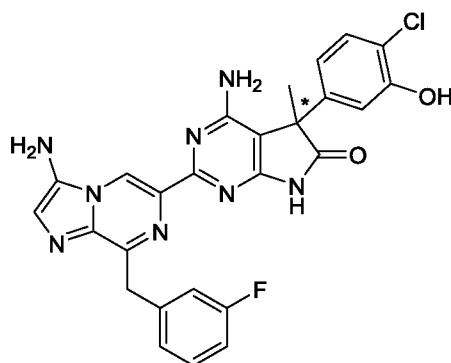
- 30 Using essentially the same procedures as described in **Example 131-AB**, the following compounds in **Table 8** were prepared. The chirality of the compounds in **Table 8** results from the use of a chiral malononitrile intermediate and/or the separation of isomers performed at **Step C**.

Table 8: Examples 131-AA -- 139-A

Ex.	Structure	Name	MS (M+1)	Int. SM / Chiral Resolution Column
131-AA		5-(4-chloro-3-hydroxyphenyl)- 2-{8-[(3- fluorophenyl)methyl]imidazo[1, 2- <i>a</i>]pyrazin-6-yl}-5-methyl-4- [(3,3,3-trifluoro-2- hydroxypropyl)amino]-5,7- dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	628	I-12A / Phenomene x Lux 5u Cellulose-4
132-AA		5-(4-chloro-3-hydroxyphenyl)- 2-{8-[(4- fluorophenyl)methyl]imidazo[1, 2- <i>a</i>]pyrazin-6-yl}-5-methyl-4- [(3,3,3-trifluoro-2- hydroxypropyl)amino]-5,7- dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	628	I-12A / Phenomene x Lux 5u Cellulose-4
132-AB		5-(4-chloro-3-hydroxyphenyl)- 2-{8-[(4- fluorophenyl)methyl]imidazo[1, 2- <i>a</i>]pyrazin-6-yl}-5-methyl-4- [(3,3,3-trifluoro-2- hydroxypropyl)amino]-5,7- dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	628	I-12A / Phenomene x Lux 5u Cellulose-4
133-AA		5-(4-chloro-3-hydroxyphenyl)- 5-methyl-2-(8-(3,3,4,4,4- pentafluorobutyl)- [1,2,4]triazolo[1,5- <i>a</i>]pyrazin-6- yl)-4-[(3,3,3-trifluoro-2- hydroxypropyl)amino]-5,7- dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	667	I-12A / CHIRALP AK IC
133-AB		5-(4-chloro-3-hydroxyphenyl)- 5-methyl-2-(8-(3,3,4,4,4- pentafluorobutyl)- [1,2,4]triazolo[1,5- <i>a</i>]pyrazin-6- yl)-4-[(3,3,3-trifluoro-2- hydroxypropyl)amino]-5,7- dihydro-6 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-6-one	667	I-12A / CHIRALP AK IC

134-A		5-(4-chloro-3-hydroxyphenyl)-2-{{8-[(4-fluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-4-(4-methylpiperazin-1-yl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	599	I-12A
135-B		4-(4,4-difluoropiperidin-1-yl)-2-{{8-[(4-fluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-(3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	586	I-17B
136-A		5-(4-chloro-3-hydroxyphenyl)-4-(4,4-difluoropiperidin-1-yl)-2-{{8-[(4-fluorophenyl)methyl]imidazo[1,2-a]pyrazin-6-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	620	I-12A
137-A		5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-4-(4-(trifluoromethyl)piperidin-1-yl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	691	I-12A
138-A		5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-4-((3,3,3-trifluoropropyl)amino)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	651	I-12A
139-A		5-(4-chloro-3-hydroxyphenyl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-a]pyrazin-6-yl)-4-((4,4,4-trifluorobutyl)amino)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	665	I-12A

EXAMPLE 140-A

4-Amino-2-(3-amino-8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one**Step A- 4-Amino-2-(3-bromo-8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl)-5-(4-chloro-3-methoxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one:**

Into a flask were placed 4-amino-5-(4-chloro-3-methoxyphenyl)-2-{8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (200 mg, 0.38 mmol), (prepared as in **Example 1-A, Step A**) in DMF (10 mL) and NBS (74 mg, 0.42 mmol) at 0 °C. The mixture was stirred at RT for 1 h, then quenched with sat. aq. sodium thiosulphate (50 mL), and extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine (30 mL), dried over anhydr. Na₂SO₄ and the filtrate concentrated *in vacuo* to dryness. The residue was purified by column chromatography with EtOAc/petroleum ether (40%~90%) to afford the title compound.

Step B- 4-amino-5-(4-chloro-3-methoxyphenyl)-2-(3-((diphenylmethylene)amino)-8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one: Into a microwave vial under an inert atmosphere of N₂ were placed intermediate from **Step A** (200 mg, 0.33 mmol), diphenylmethanimine (119 mg, 0.66 mmol), sodium *tert*-butoxide (63.1 mg, 0.66 mmol), and 2nd Generation XantPhos precatalyst (29 mg, 0.033 mmol) in dioxane (5 mL). The reaction mixture was irradiated with microwave radiation at 150 °C for 1 h, then cooled, quenched with sat., aq. NH₄Cl (50 mL), and extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine (30 mL), dried over anhydr. Na₂SO₄ and the filtrate concentrated *in vacuo* to dryness to afford the title compound, which was used directly.

Step C- 4-amino-2-(3-amino-8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl)-5-(4-chloro-3-methoxyphenyl)-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one:

Into a flask were placed intermediate from **Step B** (250 mg, 0.35 mmol) in THF(10 mL) and

water (5 mL), followed by HCl (37%, 1 mL). The reaction mixture was stirred at RT for 1 h and then the basicity of the solution was adjusted to pH8 with sat., aq. NaHCO₃. The mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layer was washed with brine (20 mL), dried over anhydr. Na₂SO₄ and the filtrate concentrated *in vacuo*. The residue was purified by RP-HPLC with MeCN/water (0.1% v/v TFA, 50%~90%) to afford the title compound.

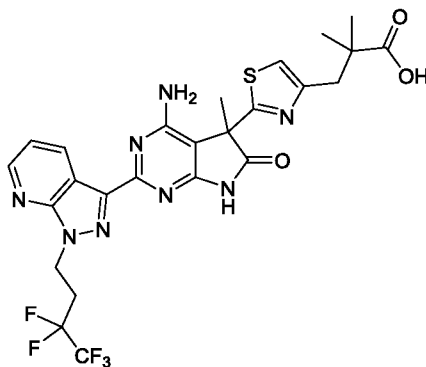
Step D-4-Amino-2-(3-amino-8-[(3-fluorophenyl)methyl]imidazo[1,2-*a*]pyrazin-6-yl)-5-(4-chloro-3-hydroxyphenyl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one:

Into a flask were placed intermediate from **Step C** (80 mg, 0.088 mmol), and hydrobromic acid (40%, 10 mL) and the mixture was stirred at 80 °C for 16 h, then at 100 °C for 6 h. It was cooled and the acidity was adjusted to pH7 with NaHCO₃ (solid), followed by the extraction with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (10 mL), dried over Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by RP-HPLC with MeCN/Water (0.1% TFA, 25%~45%) followed by silica gel column chromatography with MeOH/DCM (3%~5%) to afford the title compound, **140-A**. MS: 531 (M + 1). ¹H NMR (400 MHz, CD₃OD) δ 9.08 (s, 1H), 7.32-7.20 (m, 5H), 6.93-6.83 (m, 3H), 4.56 (s, 2H), 1.86 (s, 3H).

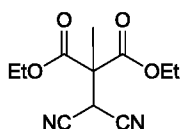
REFERENCE EXAMPLE - COMPOUND B

3-(2-{4-Amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid

This example describes the preparation of **Compound B**, which is radiolabeled and then used in the binding assay described in Biological Assays section below.



Step A - Diethyl 2-(dicyanomethyl)-2-methylmalonate:



Using the procedure described in WO2015/088885 diethyl 2-(dicyanomethyl)-2-methylmalonate was prepared. ¹H NMR (500 MHz, CDCl₃): δ 4.55 (1 H, s), 4.28-4.39 (4 H, m), 1.82 (3 H, s), 1.34 (6 H, t, *J* = 7.12 Hz).

Step B- Ethyl 4-cyano-5-ethoxy-3-methyl-2-oxo-2,3-dihydro-1H-pyrrole-3-carboxylate:

5 To a flask containing diethyl 2-(dicyanomethyl)-2-methylmalonate (20g, 84 mmol) in EtOH (280 mL) at RT was added sodium ethoxide (37.6 mL, 101 mmol, 21 wt.% in EtOH) and the mixture was stirred at 65 °C overnight. The reaction was allowed to cool down to RT and concentrated *in vacuo* to dryness. The residue was diluted with DCM and the pH value of the solution was adjusted to 7 with AcOH. The solids were removed by filtration. The resulting
10 mixture was concentrated under vacuum. The residue was purified by silica gel chromatography using an EtOAc :hexane gradient to afford the racemic title product. The racemic material was resolved using chiral SFC (CHIRALPAK[®] AS-H column) to afford isomers **I-RefA** (faster eluting) and **I-RefB** (slower eluting).

Step C- 1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-*b*]pyridine-3-carbonitrile: In a
15 flask containing 1H-pyrazolo[3,4-*b*]pyridine-3-carbonitrile (5 g, 34.7 mmol) in acetonitrile (75 mL) was added 1,1,1,2,2-pentafluoro-4-iodobutane (9.82 mL, 69.4 mmol) and potassium carbonate (24.0 g, 173 mmol). The reaction was stirred at 45 °C for 18 hours then cooled to RT, diluted with water and extracted with EtOAc (3X). The organic layers were combined, dried over anhydr. Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue
20 was purified by silica gel column chromatography with EtOAc:Hex (0-100%) to afford the title compound

Step D- 1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-*b*]pyridine-3-carboximidamide:
In a flask containing 1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-*b*]pyridine-3-carbonitrile (5.1 g, 17.7 mmol) in MeOH (11 mL) at RT was added NaOMe (1.34 g, 24.7
25 mmol). The mixture was stirred at RT for 3 h before acetic acid (4.05 mL, 70.7 mmol) was added, followed by ammonium chloride (1.23 g, 23.0 mmol). The resulting slurry was heated to 65 °C for 4 h then cooled to RT, quenched by the addition of aq. sat. NaHCO₃ and extracted with EtOAc (3X). The organic layers were combined, washed with brine dried over anhydr. Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was
30 purified by silica gel column chromatography with (EtOAc:MeOH 10:1):hexane gradient to afford the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.45 (s, 3H), 8.77 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.56 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.53 (dd, *J* = 8.3, 4.5 Hz, 1H), 4.93 (t, *J* = 6.8 Hz, 2H), 3.06 (tt, *J* = 19.1, 6.9 Hz, 2H); *m/z*=308 (M+1).

Step E- Ethyl 4-amino-5-methyl-6-oxo-2-(1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine-5-carboxylate:

To a mixture of 1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-*b*]pyridine-3-carboximidamide (1.0 g, 3.2 mmol) and **I-RefB** (1.16 g, 4.88 mmol) in THF (65 mL) at RT was added triethylamine (1.3 mL, 9.76 mmol). The resulting mixture was warmed at 65 °C for 16 h. The reaction was cooled to RT concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using MeOH:DCM (1-10%) to afford the title compound. m/z = 500 (M+1).

Step F- 4-amino-5-methyl-6-oxo-2-(1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-

***b*]pyridin-3-yl)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide:** In a sealed tube containing ethyl 4-amino-5-methyl-6-oxo-2-(1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine-5-carboxylate (1.5 g, 3.00 mmol) was added ammonia (30 mL, 3 N in MeOH). The resulting mixture was warmed at 40 °C for 16 h. The reaction was cooled to RT concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using MeOH:DCM (5%) to afford the title compound. m/z = 471 (M+1).

Step G- 4-amino-5-methyl-6-oxo-2-(1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-

***b*]pyridin-3-yl)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine-5-carbothioamide:** Into a flask was placed 4-amino-5-methyl-6-oxo-2-(1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide (1.1 g, 2.34 mmol), Lawesson's Reagent (1.1 g, 2.81 mmol) and toluene (67 mL). The resulting mixture was warmed at 80 °C for 16 h. The reaction was quenched by the addition of aq. sat. NaHCO₃, extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with MeOH:DCM (5%) to afford the title compound. m/z = 487 (M+1).

Step H- ethyl 3-(2-(4-amino-5-methyl-6-oxo-2-(1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl)thiazol-4-yl)-2,2-dimethylpropanoate:

In a sealed tube containing 4-amino-5-methyl-6-oxo-2-(1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidine-5-carbothioamide (60 mg, 0.123 mmol) and ethyl 5-bromo-2,2-dimethyl-4-oxopentanoate (48.9 mg, 0.185 mmol) in EtOH (1.2 mL) was warmed at 80 °C for 16 h. The reaction was cooled to RT concentrated *in vacuo* to dryness. The residue was purified by

silica gel chromatography using (EtOAc:EtOH 3:1): Hexane to afford the title compound. m/z = 639 (M+1).

Step I- 3-(2-{4-amino-5-methyl-6-oxo-2-(1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}thiazol-4-yl)-2,2-

- 5 **dimethylpropanoic acid:** Into a flask was placed ethyl 3-(2-(4-amino-5-methyl-6-oxo-2-(1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl)thiazol-4-yl)-2,2-dimethylpropanoate (130 mg, 0.12 mmol), LiOH (29 mg, 1.22 mmol) dioxane (2.2 mL) and water (2.2 mL) The resulting mixture was stirred at 60°C for 16 h. The reaction was cooled to RT conc. *in vacuo* then diluted in EtOAc and water and
10 acetic acid (84 μ l, 1.46 mmol) was added. The resulting solution was extracted with EtOAc. The organic layer was washed with brine, dried over anhydr. MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with (EtOAc:EtOH 3:1): hexane to afford the title compound ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.23 (s, 1H), 11.45 (s, 1H), 9.02 (dd, J = 8.1, 1.7 Hz, 1H), 8.63 (dd, J =
15 4.5, 1.6 Hz, 1H), 7.37 (dd, J = 8.1, 4.5 Hz, 1H), 7.24 (s, 1H), 6.96 (s, 2H), 4.87 (t, J = 6.8 Hz, 2H), 3.06 – 2.85 (m, 4H), 1.80 (s, 3H), 1.08 (s, 6H); m/z = 611 (M+1).

BIOLOGICAL ASSAYS:

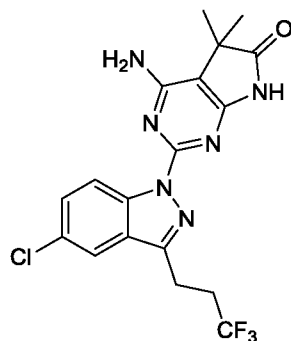
Cell-based sGC Functional Assay (cyclic GMP assay for sGC activator: CASA Assay)

- 20 Soluble guanylate cyclase (sGC) is a heme-containing enzyme that converts GTP to secondary messenger cGMP. Increases in cGMP levels affect several physiological processes including vasorelaxation through multiple downstream pathways. The rate by which sGC catalyzes cGMP formation is greatly increased by NO and by recently discovered NO-independent activators and stimulators. Heme-dependent activators (HDAs) preferentially
25 activate sGC containing a ferrous heme group. To determine the effect of sGC activators on enzyme activity, the CASA assay was developed to monitor the generation of cGMP in a cell line that stably expresses the heterodimeric sGC protein.

- Methods: A CHO-K1 cell line stably expressing the sGC $\alpha 1/\beta 1$ heterodimer was generated using a standard transfection protocol. The cDNA's encoding human sGC $\alpha 1$ and
30 $\beta 1$ were cloned in pIRES hyg and pIRES neo respectively using standard molecular biology techniques. The plasmids pIRES hyg and pIRES neo plasmids were obtained from Clontech. CHO-K1 cells were transfected with plasmids pIRES_{hyg}-hsGC $\alpha 1$ and pIRES_{neo}-hsGC $\beta 1$ simultaneously using FUGENE reagent. Clones that stably express both subunits were

selected with hygromycin and neomycin for ~2 weeks. The clone chosen for the assay was designated CHO-K1/sGC. CHO-K1/sGC cells were maintained in F-K12 medium containing 10% heat-inactivated Fetal Bovine Serum (FBS), 100 µg/mL penicillin/streptomycin, 0.5 mg/mL hygromycin and 0.25 mg/mL G418. The cells were then cryopreserved in liquid nitrogen. On the day of the assay, the cells were thawed and resuspended in EBSS Assay Buffer (Sigma, E3024) supplemented with 5 mM MgCl₂, 10 mM HEPES (4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid) and 0.05% BSA (bovine serum albumin) and cell density was then adjusted to 2.25X10⁵/mL with EAB. IBMX (3-isobutyl-1-methylxanthin, 0.5 mM) was added to inhibit degradation of cGMP. Compounds were diluted from DMSO stock solutions and added to the assay at a final DMSO concentration of 2.5%. Cells were pre-incubated in the presence and absence of 1 µM of Diethylenetriamine/nitric oxide adduct (DETA-NO; Sigma, 17018) for 30 min at 25 °C. Compounds were subsequently added and incubated for 1 hr at 37 °C. At the end of the incubation period, the reaction was terminated and the cells were lysed with the detection reagents from Cisbio Kits. The level of intracellular cGMP was determined using an HTRF-based assay kit (CisBio, 62GM2PEC), which detects the displacement of a fluorescence labeled cGMP from its specific antibody. The cGMP produced by test compounds was directly compared to the maximum cGMP production (this value was set to equal 100% activation) of the published sGC-HDA **compound A** (Example 1 in WO 2010/065275, published June 10, 2010).

Compound A



The test compounds' activities were then expressed as a percentage of compound A, the standard in every experiment. This percent activation was calculated either in the presence or absence of DETA-NO which was then plotted. Inflection points (IP) and maximum fold induction was derived using Abase analysis software for 4P fit.

Most preferred compounds had an IP of less than or equal to about 5000 nM. Data for the compounds of the Examples is provided in **Table 9**.

Table 9

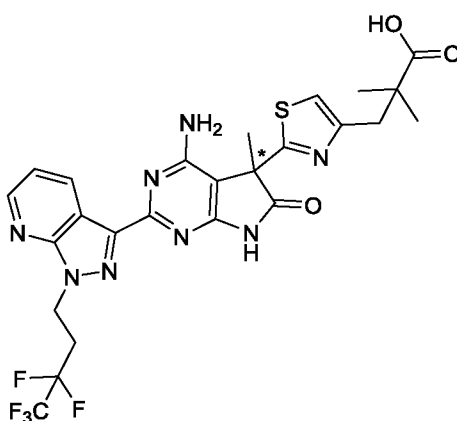
EXAMPLE	IP (nM)	% Activation		EXAMPLE	IP (nM)	% Activation
1-A	226	118		74-B	131	122
2-B	1619	89		75-B	770	153
3-B	2080	98		76-B	547	110
4-B	1925	136		77-B	645	99
5-B	188	113		78-B	202	93
6-B	94	113		79-B	96	108
7-B	217	102		80-B	19	70
8-A	316	72		81-B	352	131
9-B	1042	85		82-B	207	111
10-B	25	132		83-B	222	109
11-B	503	137		84-B	313	121
12-B	98	116		85-B	605	130
13-B	821	100		86-B	166	122
14-A	144	68		87-A	935	111
15-B	771	107		88-A	279	95
16-B	308	94		89-B	809	127
17-B	482	117		90-A	94	138
18-B	950	88		91-A	75	141
19-A	78	152		92-B	2862	104
20-A	127	130		93-B	683	98
21-B	95	143		94-B	1257	125
22-B	74	128		95-A	1812	96
23-B	3105	76		96-B	138	169
24-B	752	88		97-B	1078	138
25-A	223	117		98-B	3301	73
26-A	426	105		99-A	553	97
27-B	489	94		100-A	652	106
28-B	433	141		101-B	282	53

29-B	67	80		102-B	382	73
30-A	866	88		103-B	231	78
31-B	82	93		104-B	813	144
32-B	648	107		105-B	138	108
33-B	260	111		106-A	902	81
34-B	243	111		107-B	198	135
35-B	402	147		108-AA	198	118
36-A	381	116		108-AB	210	127
37-B	69	117		109-A	221	97
38-B	720	92		110-B	437	159
39-B	873	101		111-B	1545	86
40-B	368	88		112-B	16	112
41-B	588	136		113-A	125	91
42-B	146	170		114-B	137	112
43-B	142	101		115-B	63	79
44-A	460	100		116-B	95	137
45-A	1571	120		117-B	109	94
46-B	893	117		118-B	457	103
47-B	70	103		119-B	681	75
48-B	198	114		120-BA	85	133
49-A	363	111		120-BB	39	121
50-A	70	175		121-B	369	120
51-B	1020	88		122-B	1818	106
52-A	144	85		123-B	768	107
53-B	771	144		124-B	224	113
54-B	42	72		125-B	601	164
55-A	969	113		126-B	391	206
56-B	627	101		127-B	9980	118
57-B	798	67		128-B	1205	137
58-B	164	121		129-B	1885	84
59-B	335	109		130-A	1923	81
60-B	4383	138		131-AA	427	89

61-B	121	105		131-AB	292	96
62-B	49	97		132-AA	746	99
63-A	600	121		132-AB	736	95
64-B	1323	125		133-AA	1286	38
65-A	797	85		133-AB	3376	48
66-B	2149	141		134-A	333	102
67-A	728	134		135-B	966	103
68-B	46	96		136-A	511	66
69-A	1376	108		137-A	744	99
70-B	32	81		138-A	169	65
71-B	30	81		139-A	349	68
72-B	3457	84		140-A	816	101
73-A	694	81				

Binding assay: The binding potencies of sGC compounds to the human recombinant sGC enzyme were determined in a Size Exclusion Chromatography (SEC) competition binding assay using [³H] **Compound B** as the radioligand. [³H] **Compound B** was prepared using a standardardized tritium exchange procedure. The parent (non-labeled) molecule was first iodinated then a Pd-catalyzed iodine to tritium exchange provided the labeled compound.

Compound B



Method: The binding buffer was composed of 50 mM triethanolamine pH 7.4, 3 mM MgCl₂, 0.025 % BSA, 2 mM dithiothreitol (DTT), 300 μM DETA/NO and 400 μM GTP. Assays were conducted in 96-well plates in a total volume of 200 μL. Recombinant human sGC protein (40 ng) was incubated with 1.6 nM [³H] **Compound B** for 24 h at 37 °C in the presence and absence of various concentrations of sGC testing compounds delivered as

DMSO solutions to give a total of 1% organic solvent content. Non-specific binding was defined by competition with 1 μ M of **Compound B**. After the incubation period, the binding mixtures were loaded onto the gel-filtration plate (ThermoFischer Cat. No. 89808) pre-equilibrated with binding buffer and spun at 1000xg for 3 min at 4 °C on a Bench top centrifuge. The collected eluates in White Frame Clear Well Isoplates (Perkin Elmer Cat # 6005040) received 100 μ l of UltimaGold scintillation cocktail. The sealed plates were shaken vigorously and span, and counted after 6 hs with a Wallac Microbeta TriLux 1450 LSC & Luminescence Counter (Perkin Elmer). Data from competition experiments were analyzed to determine K_i values using one site – fit K_i equation.

Most preferred compounds had an K_i of less than or equal to about 15 nM. Data for the compounds of the Examples is provided in **Table 10**.

Table 10

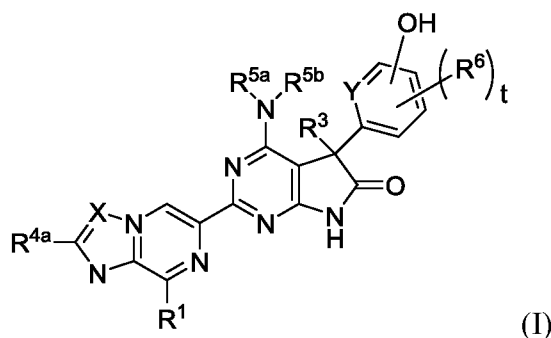
EXAMPLE	K_i (nM)		EXAMPLE	K_i (nM)
1-A	0.095		74-B	6.174
2-B	0.095		75-B	6.553
3-B	0.219		76-B	7.888
4-B	0.259		77-B	8.795
5-B	0.091		78-B	8.877
6-B	0.094		79-B	9.413
7-B	0.098		80-B	9.985
8-A	0.117		81-B	13.95
9-B	0.126		82-B	0.402
10-B	0.128		83-B	5.122
11-B	0.135		84-B	3.460
12-B	0.153		85-B	4.817
13-B	0.154		86-B	2.222
14-A	0.156		87-A	2.799
15-B	0.158		88-A	2.500
16-B	0.158		89-B	0.823
17-B	0.163		90-A	2.434
18-B	0.168		91-A	0.199

19-A	0.170		92-B	0.729
20-A	0.173		93-B	0.374
21-B	0.206		94-B	0.149
22-B	0.214		95-A	14.39
23-B	0.216		96-B	0.862
24-B	0.241		97-B	0.587
25-A	0.252		98-B	8.309
26-A	0.276		99-A	0.803
27-B	0.280		100-A	0.544
28-B	0.283		101-B	0.162
29-B	0.291		102-B	0.118
30-A	0.292		103-B	0.175
31-B	0.274		104-B	1.100
32-B	0.306		105-B	0.213
33-B	0.312		106-A	1.837
34-B	0.317		107-B	0.221
35-B	0.333		108-AA	0.924
36-A	0.393		108-AB	0.524
37-B	0.427		109-A	0.634
38-B	0.410		110-B	1.625
39-B	0.446		111-B	1.740
40-B	0.479		112-B	1.776
41-B	0.490		113-A	2.897
42-B	0.496		114-B	4.950
43-B	0.457		115-B	5.026
44-A	0.507		116-B	6.375
45-A	0.565		117-B	8.552
46-B	0.691		118-B	7.952
47-B	0.676		119-B	2.764
48-B	0.723		120-BA	10.86

49-A	0.746		120-BB	3.786
50-A	0.775		121-B	0.382
51-B	0.874		122-B	15.61
52-A	0.864		123-B	0.372
53-B	1.076		124-B	2.632
54-B	1.082		125-B	0.508
55-A	1.211		126-B	1.099
56-B	1.237		127-B	9.721
57-B	1.242		128-B	0.646
58-B	1.539		129-B	1.995
59-B	1.716		130-A	7.149
60-B	1.915		131-AA	0.884
61-B	2.085		131-AB	0.347
62-B	2.208		132-AA	1.209
63-A	2.200		132-AB	1.459
64-B	2.222		133-AA	2.336
65-A	2.257		133-AB	9.245
66-B	2.569		134-A	0.592
67-A	2.652		135-B	4.011
68-B	2.920		136-A	1.566
69-A	3.471		137-A	2.629
70-B	3.957		138-A	4.622
71-B	4.076		139-A	3.544
72-B	4.615		140-A	0.827
73-A	6.014			

CLAIMS

1. A compound of the Formula (I)



or a pharmaceutically acceptable salt thereof, wherein:

X is C(R^{4b}) or N;

Y is C(H) or N;

R¹ is:

- (a.) (C₁-C₃)alkyl-R²,

R² is phenyl, C₃-C₈ cycloalkyl, or C₅-C₇ cycloalkenyl, wherein R² is

unsubstituted or substituted by 1 to 3 R^{2a};

each R^{2a} is independently halo, (C₁-C₃)alkyl, or (C₁-C₃)fluoroalkyl; or

- (b.) (C₁-C₆)alkyl, wherein said alkyl is unsubstituted or substituted by 1 to 6 fluoro;

R³ is (C₁-C₃)alkyl or (C₃-C₆)cycloalkyl;

R^{4a} is H or (C₁-C₃)alkyl;

R^{4b} is H or NH₂;

R^{5a} and R^{5b} are independently H or (C₁-C₆)alkyl, wherein said alkyl is unsubstituted or substituted by 1 to 6 substituents independently selected from fluoro or hydroxyl; or alternatively, R^{5a} and R^{5b} together with the nitrogen atom to which they are attached form ring C⁵ which is an azetidiny, pyrrolyl, piperidiny, piperaziny, or azepiny ring, wherein ring C⁵ is unsubstituted or substituted by 1 to 3 substituents which are independently halo, hydroxyl, (C₁-C₃)alkyl, or (C₁-C₃)fluoroalkyl;

each R⁶ is independently halo, (C₁-C₃)alkyl, (C₁-C₃)fluoroalkyl, or cyano; and

the subscript t is 0, 1, 2, or 3; and

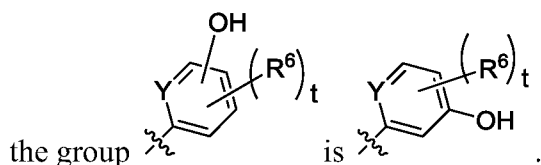
with the proviso that the compound is not:

4-amino-5-(5-hydroxypyridin-2-yl)-5-methyl-2-(8-(3,3,4,4,4-pentafluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidine-6-one;
4-amino-5-(5-hydroxypyridin-2-yl)-5-methyl-2-(8-(4,4,4-trifluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5*H*-pyrrolo[2,3-*d*]pyrimidine-6(7*H*)-one; or
4-amino-5-cyclopropyl-5-(5-hydroxypyridin-2-yl)-2-(8-(4,4,4-trifluorobutyl)-[1,2,4]triazolo[1,5-*a*]pyrazin-6-yl)-5*H*-pyrrolo[2,3-*d*]pyrimidine-6(7*H*)-one.

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein X is C(R^{4b}).
3. The compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein R^{4b} is H.
4. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein X is N.
5. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein Y is C(H).
6. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein Y is N.
7. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R¹ is (C₁-C₃)alkyl-R²,
R² is phenyl, C₃-C₈ cycloalkyl, or C₅-C₇ cycloalkenyl, wherein R² is unsubstituted or substituted by 1 to 3 R^{2a}; and
each R^{2a} is independently halo, (C₁-C₃)alkyl, or (C₁-C₃)fluoroalkyl.
8. The compound of claim 7 or a pharmaceutically acceptable salt thereof, wherein R¹ is -CH₂-R².
9. The compound of claim 8 or a pharmaceutically acceptable salt thereof, wherein R² is unsubstituted phenyl or phenyl substituted by 1 to 3 R^{2a}.

10. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R³ is methyl.
11. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R^{4a} is H.
12. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R^{5a} and R^{5b} are H.
13. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the subscript t is 0 or 1.

14. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein



15. The compound of claim 14 or a pharmaceutically acceptable salt thereof, wherein:
 X is C(H) or N;
 Y is C(H) or N;
 R¹ is -CH₂-R²,

R² is unsubstituted phenyl or phenyl substituted by 1 to 3 R^{2a};

each R^{2a} is independently halo, (C₁-C₃)alkyl, or (C₁-C₃)fluoroalkyl;

R³ is methyl;

R^{5a} and R^{5b} are H; and

the subscript t is 0 or 1.

16. The compound of claim or a pharmaceutically acceptable salt thereof, wherein the compound is any one of the compounds of Examples 1A – 140A.
17. A pharmaceutical composition comprising a therapeutically effective amount of the compound of any one of claims 1 to 16 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

18. The pharmaceutical composition of claim 17, further comprising one or more additional active agents selected from an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, a neutral endopeptidase inhibitor, an aldosterone antagonist, a renin inhibitor, an endothelin receptor antagonist, an aldosterone synthase inhibitor, a phosphodiesterase-5 inhibitor, a vasodilator, a calcium channel blocker, a potassium channel activator, a diuretic, a sympatholytic, a beta-adrenergic blocking drug, an alpha adrenergic blocking drug, a central alpha adrenergic agonist, a peripheral vasodilator, a lipid lowering agent, metabolic altering agent, a β_2 agonist, an anticholinergic, a corticosteroid or a corticosteroid analog.
19. A method for activating soluble guanylate cyclase comprising administering an amount efficacious therefor of the compound of any one of claims 1 to 16 or a pharmaceutically acceptable salt thereof.
20. A method for treating a condition selected from cardiovascular disease, endothelial dysfunction, diastolic dysfunction, atherosclerosis, hypertension, heart failure, pulmonary hypertension (WHO groups I, II, III, IV), angina pectoris, thrombosis, restenosis, myocardial infarction, stroke, cardiac insufficiency, fibrosis, pulmonary hypertonia, erectile dysfunction, asthma, chronic kidney disease, diabetes, cirrhosis of the liver, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome, acute lung injury, pulmonary fibrosis, cystic fibrosis, or interstitial lung disease, comprising administering a therapeutically effective amount of the compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.
21. A method for treating pulmonary hypertension comprising administering a therapeutically effective amount of the compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.
22. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, for use in therapy.
23. The use of the compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament useful for treating a condition selected

from cardiovascular disease, endothelial dysfunction, diastolic dysfunction, atherosclerosis, hypertension, heart failure, pulmonary hypertension (WHO groups I, II, III, IV), angina pectoris, thrombosis, restenosis, myocardial infarction, stroke, cardiac insufficiency, fibrosis, pulmonary hypertonia, erectile dysfunction, asthma, chronic kidney disease, diabetes, cirrhosis of the liver, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome, acute lung injury, pulmonary fibrosis, cystic fibrosis, or interstitial lung disease.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/082180

A. CLASSIFICATION OF SUBJECT MATTER

C07D 487/04(2006.01)i; A61K 31/519(2006.01)i; A61P 9/00(2006.01)i; A61P 13/00(2006.01)i; A61P 25/00(2006.01)i; A61P 3/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 487/-, A61K 31/-, A61P 9/-, A61P 13/-, A61P 25/-, A61P 3/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, CNPAT, CNKI, REGISTRY, CAPLUS: imidazole, pyrazine, pyrimidine, fused, guanylate cyclase

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015187470 A1 (MERCK SHARP & DOHME CORP. ET AL.) 10 December 2015 (2015-12-10) pages 75-81	1-23
A	WO 2011149921 A1 (MERCK SHARP & DOHME CORP. ET AL.) 01 December 2011 (2011-12-01) the whole document	1-23
A	WO 2010065275 A1 (MERCK SHARP & DOHME CORP. ET AL.) 10 June 2010 (2010-06-10) the whole document	1-23

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

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

13 December 2016

Date of mailing of the international search report

30 December 2016

Name and mailing address of the ISA/CN

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Telephone No. (86-10)010-82246686

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/082180

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **19-21**
because they relate to subject matter not required to be searched by this Authority, namely:
 - [1] Claims 19-21 are directed to the methods for treating diseases, but the search is based on the use of the compound of any one of claims 1 to 16 for the preparation of medicaments for treating the corresponding diseases.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2016/082180

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2015187470	A1	10 December 2015	None			
WO	2011149921	A1	01 December 2011	EA	201291348	A1	28 June 2013
				CN	103096718	B	20 January 2016
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				MX	2012013774	A	17 December 2012
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				IL	223259	D0	03 February 2013
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				MA	34330	B1	01 June 2013
				NZ	603884	A	27 June 2014
				JP	2014055151	A	27 March 2014
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				CA	2743864	A1	10 June 2010
				JP	2012509877	A	26 April 2012
				EP	2373317	A1	12 October 2011
				AU	2009322836	A1	23 June 2011
				JP	5501369	B2	21 May 2014
				US	8741910	B2	03 June 2014