

4-AMINO-2-(1H-PYRAZOLO[3,4-B]PYRIDIN-3-YL)-6-OXO-6,7-DIHYDRO-5H-PYRROLO[2,3-D]PYRIMIDINE DERIVATIVES AND THE RESPECTIVE (1H-INDAZOL-3-YL) DERIVATIVES AS CGMP MODULATORS FOR TREATING CARDIOVASCULAR DISEASES

BACKGROUND OF THE INVENTION

Cyclic GMP (cGMP) is an important intracellular messenger which triggers a multitude of different effects via the modulation of cGMP-dependent protein kinases, phosphodiesterases and ion 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 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 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, 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.

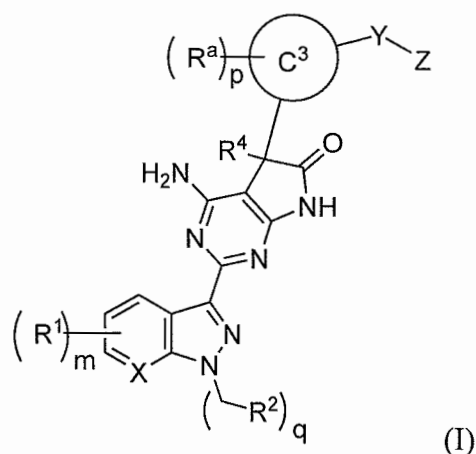
Various sGC stimulators which do not act via NO release were described by Vesely in a series of publications. However, the compounds, most of which are hormones, plant hormones, vitamins or natural compounds such as, for example, lizard poisons, predominantly only have weak effects on the cGMP formation 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 are therefore may be suitable for the therapy and prophylaxis of disorders which are associated with a low cGMP level.

SUMMARY

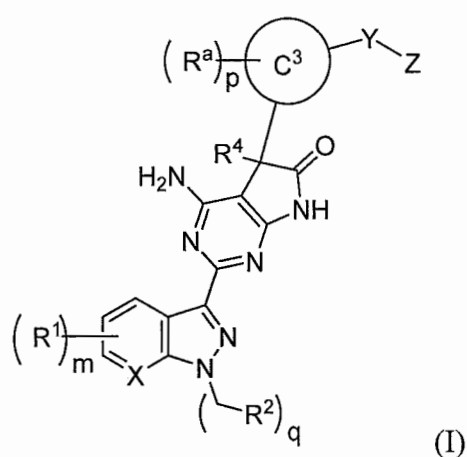
The present disclosure relates to compounds which activate soluble guanylate cyclase and may be valuable pharmaceutically active compounds for the therapy and prophylaxis of diseases, for example for cardiovascular diseases such as hypertension, heart failure, pulmonary

hypertension, angina pectoris, diabetes, cardiac insufficiency, thrombosis, chronic kidney disease, fibrosis or atherosclerosis. The compounds of Formula (I)



are capable of modulating the body's production of cyclic guanosine monophosphate ("cGMP") and may be suitable for the therapy and prophylaxis of diseases which are associated with a disturbed cGMP balance.

In one aspect, there is provided a compound of the Formula (I)



or a pharmaceutically acceptable salt thereof, wherein:

- 10 X is C(H) or N;
- each R1 is independently halo, hydroxy, C1-C3 alkyl, C3-C6 cycloalkyl or -O-C1-C3 alkyl;
- R2 is:
 - (a.) C1-C6 alkyl, wherein said C1-C6 alkyl of R2 is unsubstituted or substituted by 1 to 6 moieties independently selected from fluoro or -O-C1-C3 alkyl;
 - 15 (b.) ring C2, wherein ring C2 is:
 - (i.) C3-C12 cycloalkyl;
 - (ii.) phenyl;
 - (iii.) a 5- or 6-membered monocyclic heteroaryl containing 1 to 2 heteroatoms selected from N, O, or S; or

(iv.) a 5- or 6-membered monocyclic heterocyclyl containing 1 to 2 heteroatoms selected from N, O, or S;

wherein ring C2 is unsubstituted or substituted by 1 to 3 moieties independently selected from halo, cyano, C1-C3 alkyl, -O-C1-C3 alkyl, or oxo;

5 R4 is C1-C6 alkyl, CF3, or C3-C6 cycloalkyl;

ring C3 is:

(a.) phenyl;

(b.) a 5- or 6-membered monocyclic heteroaryl or a 9- to 10-membered bicyclic heteroaryl containing 1 to 3 heteroatoms selected from N, O, or S;

10 (c.) a 5- or 6-membered monocyclic heterocyclyl containing 1 to 3 heteroatoms selected from N, O, or S; or

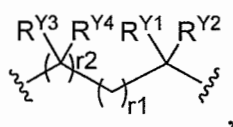
(d.) C3-C6 cycloalkyl;

each Ra is independently selected from halo, cyano, C1-C3 alkyl, -O-C1-C3 alkyl, oxo, or hydroxy;

15 Y is:

(a.) a bond;

(b.) a group of the formula

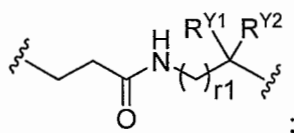


wherein RY1 and RY2 are independently H, C1-C3 alkyl, hydroxy, fluoro, C1-C3 hydroxyalkyl, or amino; or alternatively RY1 and RY2, together with the carbon atom to which they are

20 attached form a C3-C6 cycloalkyl;

RY3 and RY4 are independently H, C1-C3 alkyl, hydroxy, fluoro, or C1-C3 hydroxyalkyl; or alternatively RY3 and RY4, together with the carbon atom to which they are attached form a C3-C6 cycloalkyl;

(c.) a group of the formula

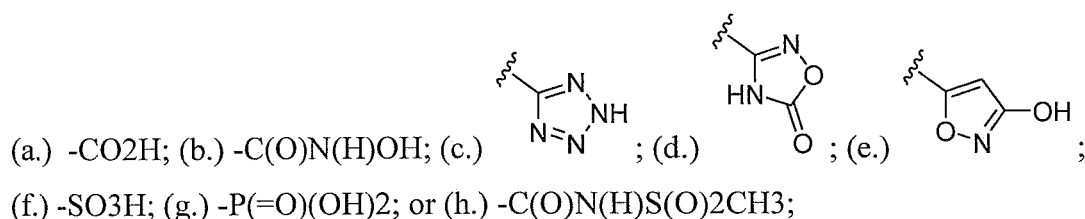


25 (d.) ring AH, wherein ring AH is C3-C6 cycloalkyl or phenyl, wherein ring AH is unsubstituted or substituted by 1 to 3 moieties independently selected from halo or C1-C3 alkyl;

(e.) a group -CH=CH-; or

(f.) a group

Z is:



the subscript m is 0, 1, or 2;

5 the subscript p is 0, 1, 2, or 3;

the subscript q is 0 or 1;

the subscript r1 is 0, 1, 2, 3, or 4; and

the subscript r2 is 0 or 1.

The disclosure furthermore relates to processes for preparing compounds of Formula (I),
10 to 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).

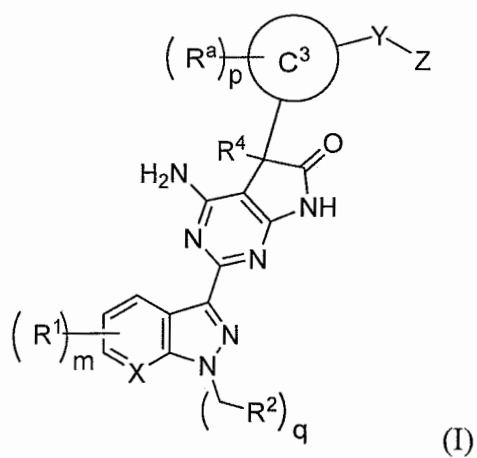
In another aspect, there is provided a pharmaceutical composition comprising the
compound as defined herein or a pharmaceutically acceptable salt thereof, and a
15 pharmaceutically acceptable carrier.

In another aspect, there is provided a compound as defined herein, or a pharmaceutically
acceptable salt thereof, for use in therapy

In another aspect, there is provided the use of the compound as defined herein, or a
pharmaceutically acceptable salt thereof, for the preparation of a medicament useful for treating
20 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, acute respiratory distress syndrome
(ARDS), chronic kidney disease, cystic fibrosis, sickle cell anemia, scleroderma, Raynaud's
25 Syndrome, diabetes, diabetic retinopathy, cirrhosis of the liver, chronic obstructive pulmonary
disease (COPD), acute lung injury, pulmonary fibrosis, or interstitial lung disease.

DETAILED DESCRIPTION OF THE INVENTION

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



5 or a pharmaceutically acceptable salt thereof, wherein:

X is C(H) or N;

each R¹ is independently halo, hydroxy, C₁-C₃ alkyl, C₃-C₆ cycloalkyl or -O-C₁-C₃ alkyl;

R² is:

- (a.) C₁-C₆ alkyl, wherein said C₁-C₆ alkyl of R² is unsubstituted or substituted by 1 to 6 moieties independently selected from fluoro or -O-C₁-C₃ alkyl;
- (b.) ring C², wherein ring C² is:
 - (i.) C₃-C₁₂ cycloalkyl;
 - (ii.) phenyl;
 - (iii.) a 5- or 6-membered monocyclic heteroaryl containing 1 to 2 heteroatoms selected from N, O, or S; or
 - (iv.) a 5- or 6-membered monocyclic heterocyclyl containing 1 to 2 heteroatoms selected from N, O, or S;

wherein ring C² is unsubstituted or substituted by 1 to 3 moieties independently selected from halo, cyano, C₁-C₃ alkyl, -O-C₁-C₃ alkyl, or oxo;

R⁴ is C₁-C₆ alkyl, CF₃, or C₃-C₆ cycloalkyl;

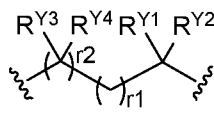
ring C³ is:

- (a.) phenyl;
- (b.) a 5- or 6-membered monocyclic heteroaryl or a 9- to 10-membered bicyclic heteroaryl containing 1 to 3 heteroatoms selected from N, O, or S;
- (c.) a 5- or 6-membered monocyclic heterocyclyl containing 1 to 3 heteroatoms selected from N, O, or S; or
- (d.) C₃-C₆ cycloalkyl;

each R^a is independently selected from halo, cyano, C₁-C₃ alkyl, -O-C₁-C₃ alkyl, oxo, or hydroxy;

Y is:

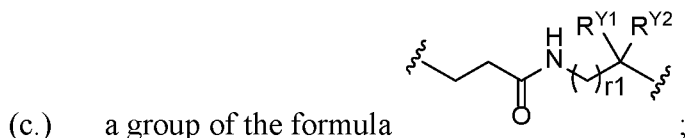
- (a.) a bond;



- (b.) a group of the formula

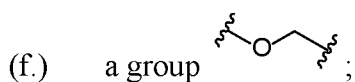
wherein R^{Y1} and R^{Y2} are independently H, C₁-C₃ alkyl, hydroxy, fluoro, C₁-C₃ hydroxyalkyl, or amino; or alternatively R^{Y1} and R^{Y2}, together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl;

R^{Y3} and R^{Y4} are independently H, C₁-C₃ alkyl, hydroxy, fluoro, or C₁-C₃ hydroxyalkyl; or alternatively R^{Y3} and R^{Y4} , together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl;

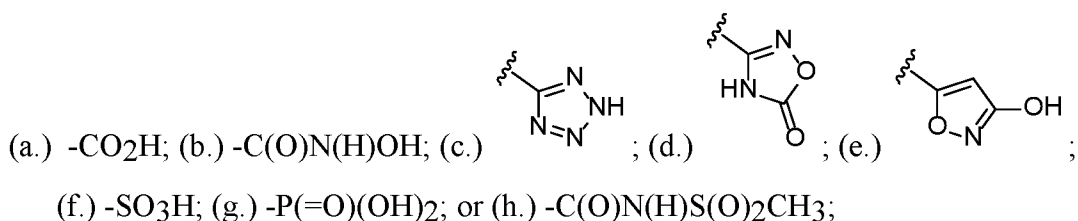


(d.) ring A^H, wherein ring A^H is C₃-C₆ cycloalkyl or phenyl, wherein ring A^H is unsubstituted or substituted by 1 to 3 moieties independently selected from halo or C₁-C₃ alkyl;

(e.) a group -CH=CH-; or



Z is:



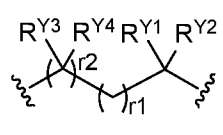
the subscript m is 0, 1, or 2;

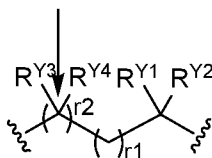
the subscript p is 0, 1, 2, or 3;

the subscript q is 0 or 1;

the subscript r₁ is 0, 1, 2, 3, or 4; and

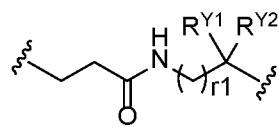
the subscript r₂ is 0 or 1.

In the compounds of Formula (I), when Y is a group of the formula  , the carbon atom bearing R^{Y3} and R^{Y4} (indicated by the arrow in the structural formula below)

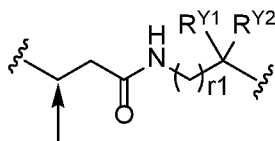


is bonded to a ring atom of ring C³, and the carbon atom bearing R^{Y1} and R^{Y2} is bonded to Z.

Similarly, in the compounds of Formula (I), when Y is a group of the formula

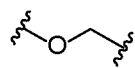


, the leftmost carbon atom (indicated by the arrow in the structural formula below)



- 5 is bonded to a ring atom of ring C³, and the carbon atom bearing R^{Y1} and R^{Y2} is bonded to Z.

Similarly, in the compounds of Formula (I), when Y is a group of the formula



, the oxygen atom of the group Y is bonded to a ring atom of ring C³, and the carbon atom in group Y is bonded to Z.

In embodiment no. 2, the present invention provides the compound having structural

- 10 Formula (I), wherein

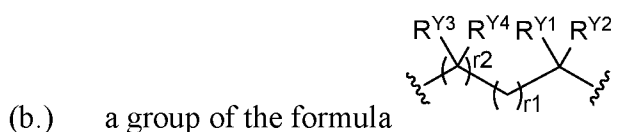
ring C³ is:

- (a.) phenyl;
- (b.) a 5- or 6-membered monocyclic heteroaryl containing 1 to 3 heteroatoms selected from N, O, or S;
- 15 (c.) a 5- or 6-membered monocyclic heterocyclyl containing 1 to 3 heteroatoms selected from N, O, or S; or
- (d.) C₃-C₆ cycloalkyl;

each R^a is independently selected from halo, cyano, C₁-C₃ alkyl, -O-C₁-C₃ alkyl, or oxo;

- 20 Y is:

- (a.) a bond;



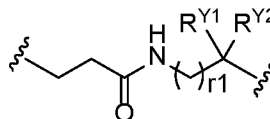
wherein R^{Y1} and R^{Y2} are independently H, C₁-C₃ alkyl, hydroxy, fluoro, or C₁-

C₃ hydroxyalkyl; or alternatively R^{Y1} and R^{Y2}, together with the carbon

- 25 atom to which they are attached form a C₃-C₆ cycloalkyl;

RY^3 and RY^4 are independently H, C_1 - C_3 alkyl, hydroxy, fluoro, or C_1 - C_3

hydroxyalkyl; or alternatively RY^3 and RY^4 , together with the carbon atom to which they are attached form a C_3 - C_6 cycloalkyl;



(c.) a group of the formula ; or

5 (d.) ring AH , wherein ring AH is C_3 - C_6 cycloalkyl or phenyl, wherein ring AH is unsubstituted or substituted by 1 to 3 moieties independently selected from halo or C_1 - C_3 alkyl; and

the remaining variables are as set forth in embodiment no. 1.

In embodiment no. 3, the present invention provides the compound having structural
10 Formula (I), wherein the subscript q is 1, and R^2 is C_2 - C_3 alkyl which is unsubstituted or substituted by 1 to 5 fluoro; and the remaining variables are as set forth in embodiment no. 2.

In embodiment no. 4, the present invention provides the compound having structural

Formula (I), wherein the subscript q is 1, and the group  R^2 is selected from
- $\text{CH}_2\text{CH}_2\text{CF}_2\text{CF}_3$, - $\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$, - $\text{CH}_2\text{CH}_2\text{CH}_3$, - $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, or
15 - $\text{CH}_2\text{CH}_2\text{OCH}_3$; and the remaining variables are as set forth in embodiment no. 2.

In embodiment no. 5, the present invention provides the compound having structural

Formula (I), wherein the subscript q is 1, and the group  R^2 is - $\text{CH}_2\text{CH}_2\text{CF}_2\text{CF}_3$; and the remaining variables are as set forth in embodiment no. 2.

In embodiment no. 6, the present invention provides the compound having structural
20 Formula (I), wherein the subscript q is 1;

R^2 is ring C^2 ;

ring C^2 is phenyl, cyclohexyl, adamantyl, pyridyl, or tetrahydropyranyl;

wherein ring C^2 is unsubstituted or independently substituted by 1 to 3 fluoro or methyl; and

25 the remaining variables are as set forth in embodiment no. 2.

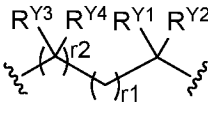
In embodiment no. 7, the present invention provides the compound having structural
Formula (I), wherein ring C^3 is phenyl, thiazolyl, oxazolyl, oxadiazolyl, triazolyl, or pyridyl; and the remaining variables are as set forth in embodiment no. 2.

In embodiment no. 8, the present invention provides the compound having structural Formula (I), wherein ring C³ is phenyl; and the remaining variables are as set forth in embodiment no. 2.

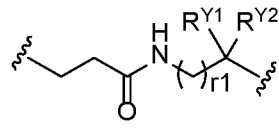
5 In embodiment no. 9, the present invention provides the compound having structural Formula (I), wherein ring C³ is thiazolyl; and the remaining variables are as set forth in embodiment no. 2.

In embodiment no. 10, the present invention provides the compound having structural Formula (I), wherein ring C³ is oxazolyl; and the remaining variables are as set forth in embodiment no. 2.

10 In embodiment no. 11, the present invention provides the compound having structural

Formula (I), wherein Y is the group of the formula , and the remaining variables are as set forth in embodiment no. 2.

In embodiment no. 12, the present invention provides the compound having structural

Formula (I), wherein Y is the group of the formula , and the remaining variables are as set forth in embodiment no. 2.

In embodiment no. 13, the present invention provides the compound having structural Formula (I), wherein Y is as set forth in embodiment nos. 11 or 12,

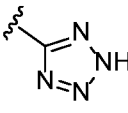
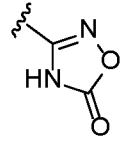
the subscript r1 is 1;

the subscript r2 is 0 (where present, as in embodiment no. 11);

20 R^{Y1} and R^{Y2} are independently H or C₁-C₃ alkyl;

the remaining variables are as set forth in embodiment no. 2.

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

Formula (I), wherein Z is (a.) -CO₂H; (b.) -C(O)N(H)OH; (c.) ; or (d.) ; and the remaining variables are as set forth in embodiment no. 2.

25 In embodiment no. 15, the present invention provides the compound having structural Formula (I), wherein Z is -CO₂H, and the remaining variables are as set forth in embodiment no. 2.

In embodiment no. 16, the present invention provides the compound having structural Formula (I), wherein the subscript m is 0 or 1, and the remaining variables are as set forth in embodiment no. 2.

5 In embodiment no. 17, the present invention provides the compound having structural Formula (I), wherein R¹ is chloro or fluoro, and the remaining variables are as set forth in embodiment no. 2.

In embodiment no. 18, the present invention provides the compound having structural Formula (I), wherein X is C(H); and the remaining variables are as set forth in embodiment no. 2.

10 In embodiment no. 19, 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. 2.

In embodiment no. 20, the present invention provides the compound having structural Formula (I), wherein R⁴ is methyl or cyclopropyl, and the remaining variables are as set forth in embodiment no. 2.

15 In embodiment no. 21, the present invention provides the compound having structural Formula (I), wherein R⁴ is methyl, and the remaining variables are as set forth in embodiment no. 2.

In embodiment no. 22, the present invention provides the compound having structural Formula (I), wherein

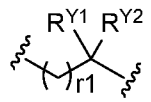
20 R² is C₂-C₃ alkyl which is unsubstituted or substituted by 1 to 5 fluoro;
ring C³ is as set forth as in embodiment no. 7;
Y is as set forth in embodiment no. 11;
Z is as set forth in embodiment no. 14;
R¹ is chloro or fluoro;
X is C(H) or N;
25 R⁴ is methyl or cyclopropyl;
the subscript m is 0 or 1;
the subscript q is 1; and
R_a, R_{Y1}, R_{Y2}, R_{Y3}, R_{Y4} and the subscripts p, r₁, and r₂ are as set forth in embodiment
no. 2.

30 In embodiment no. 23, the present invention provides the compound having structural Formula (I), wherein

the group  R^2 is $-\text{CH}_2\text{CH}_2\text{CF}_2\text{CF}_3$:

ring C^3 is as set forth as in embodiment no. 8, 9, or 10;

R^a is fluoro, chloro, cyano, methyl, methoxy, or oxo;

Y is ;

5 $\text{R}^{\text{Y}1}$ and $\text{R}^{\text{Y}2}$ are independently H or $\text{C}_1\text{-C}_3$ alkyl;

Z is $-\text{CO}_2\text{H}$;

R^1 is chloro or fluoro;

X is $\text{C}(\text{H})$ or N ;

R^4 is methyl;

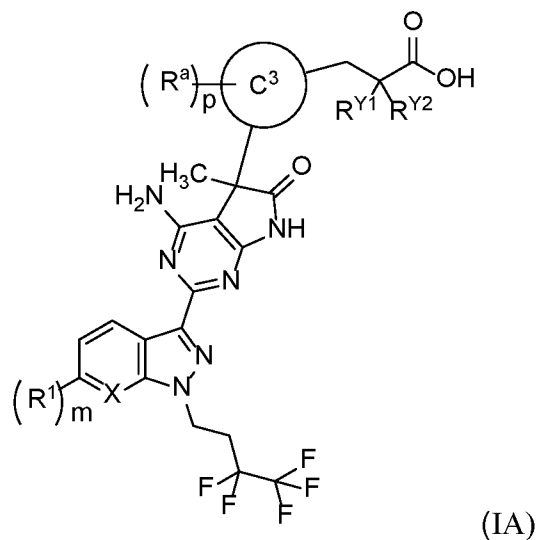
10 the subscript m is 0 or 1;

the subscript p is 0, 1, or 2;

the subscript q is 1; and

the subscript $r1$ is 1.

In embodiment no. 24, the compound of the Formula (I) has the Formula (IA)



wherein

X is $\text{C}(\text{H})$ or N ;

R^1 is methyl or halo;

C^3 is phenyl or thiazolyl;

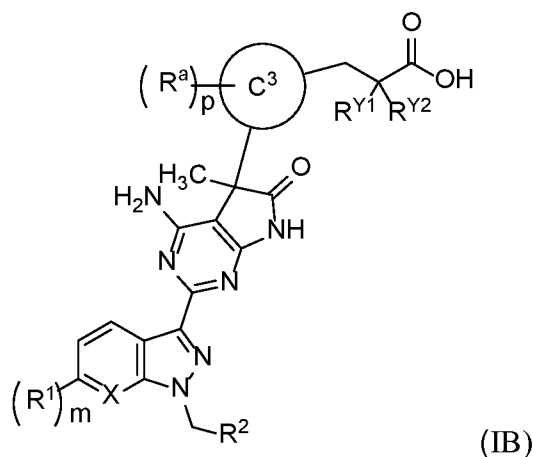
20 R^a is methyl, cyano, or halo;

RY1 and RY2 are independently H or methyl;

the subscript m is 0 or 1; and

the subscript p is 0 or 1.

In embodiment no. 25, the compound of the Formula (I) has the Formula (IB)



wherein

X is C(H) or N;

R1 is methyl or halo;

R2 is ring C2, wherein ring C2 is:

(i.) C₃-C₁₂ cycloalkyl;

(ii.) phenyl;

(iii.) a 5- or 6-membered monocyclic heteroaryl containing 1 to 2 heteroatoms selected from N, O, or S; or

(iv.) a 5- or 6-membered monocyclic heterocyclyl containing 1 to 2 heteroatoms selected from N, O, or S;

wherein ring C2 is unsubstituted or substituted by 1 to 3 moieties independently selected from halo, cyano, C₁-C₃ alkyl, -O-C₁-C₃ alkyl, or oxo;

C³ is phenyl, thiazolyl, or oxazolyl;

R^a is methyl, cyano, or halo;

RY1 and RY2 are independently H or methyl;

the subscript m is 0 or 1; and

the subscript p is 0 or 1.

In embodiment no. 26, the present invention provides a compound having the Formula (IB), wherein

R² is phenyl which is unsubstituted or substituted by 1 to 3 moieties independently selected from halo, cyano, C₁-C₃ alkyl, or -O-C₁-C₃ alkyl; and

the remaining variables are as set forth in embodiment no. 25.

In embodiment no. 27, the present invention provides a compound having the Formula

5 (IA), wherein

R¹ is halo;

C³ is phenyl, thiazolyl, oxazolyl, or benzothiazolyl;

RY¹ and RY² are independently H, methyl, or amino; and

X, R^a, and the subscripts m and p are as set forth in embodiment no. 24.

10 In embodiment no. 28, the present invention provides a compound having the Formula (IB), wherein

R¹ is halo;

C³ is phenyl, thiazolyl, oxazolyl, or benzothiazolyl;

RY¹ and RY² are independently H, methyl, or amino; and

15 X, R², R^a, and the subscripts m and p are as set forth in embodiment no. 25.

In embodiment no. 29, the present invention provides the compound having the formula (IB), wherein R² is phenyl and

X, R¹, C³, R^a, RY¹, RY², the subscripts m and p are as set forth in embodiment no. 25.

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

20 3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

25 3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-bromophenyl)propanoic acid;

3-{4-[4-amino-2-{6-chloro-1-[(4-methylcyclohexyl)methyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

30 3-{4-[4-amino-2-{6-chloro-1-[tetrahydro-2*H*-pyran-2-ylmethyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

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

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

5 dimethylpropanoic acid;

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

10 3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

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

15 3-(4-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)propanoic acid;

3-(4-{4-amino-2-(1-butyl-6-chloro-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

20 3-(4-{4-amino-2-(1-butyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-5-methyl-6-oxo-2-[1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

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

25 3-(4-{4-amino-5-methyl-6-oxo-2-[1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2-methylpropanoic acid;

3-(4-{4-amino-2-[5-fluoro-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

30 3-(4-{4-amino-2-[6-chloro-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-5-methyl-2-[6-methyl-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(3-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

5 3-(4-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(3-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

10 3-(4-{4-amino-2-[1-(2,3-difluoro-4-methylbenzyl)-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}benzoic acid;

15 3-(3-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)acetic acid;

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)propanoic acid;

20 2-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)-2-methylpropanoic acid;

25 3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)-2,2-dimethylpropanoic acid;

1-[(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)methyl]cyclopropanecarboxylic acid;

30 3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2-methylpropanoic acid;

2-{4-[4-amino-2-(1-butyl-6-chloro-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1*H*-1,2,3-triazol-1-yl}acetic acid;

3-{4-[4-amino-2-(1-butyl-6-chloro-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1*H*-1,2,3-triazol-1-yl}propanoic acid;

5 3-{4-[4-amino-2-(1-butyl-6-chloro-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}-2,2-dimethylpropanoic acid;

3-{4-[4-amino-2-(1-butyl-6-chloro-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

10 3-(3-{4-amino-2-[6-chloro-1-(2-methoxyethyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(2-methoxyethyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(4,4,4-trifluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

15 3-(4-{4-amino-2-[6-chloro-1-(4,4,4-trifluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

3-{4-[4-amino-2-(6-chloro-1-pentyl-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

20 3-(4-{4-amino-2-[6-chloro-1-(cyclohexylmethyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-{4-[4-amino-2-(6-chloro-1-hexyl-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

3-(4-{4-amino-2-[6-fluoro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

25 3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(3-{4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

30 4-(2-{4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}thiazol-4-yl)butanoic acid;

3-(2-{4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)propanoic acid;

2-(2-{4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)acetic acid;

3-(4-{4-amino-2-[6-chloro-1-(4,4-dimethylpentyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

5 3-(3-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)propanoic acid;

10 4-(2-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}thiazol-4-yl)butanoic acid;

3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

3-(4-[4-amino-2-{6-chloro-1-[(3-fluoropyridin-2-yl)methyl]-1*H*-indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl)propanoic acid;

15 3-(4-[4-amino-2-{6-chloro-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl)propanoic acid;

3-(4-{4-amino-2-[1-(2-fluorobenzyl)-6-methyl-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

20 3-(4-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(3-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(2-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

25 3-(2-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

30 3-(4-{4-amino-2-[6-chloro-1-(4-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

- 3-(4-{4-amino-2-[6-chloro-1-(4-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;
- 3-(4-{4-amino-2-[6-chloro-1-(2-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;
- 5 3-(4-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;
- 3-(4-{2-[1-(adamantan-1-ylmethyl)-6-chloro-1*H*-indazol-3-yl]-4-amino-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;
- 3-(4-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;
- 10 3-(2-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;
- 3-(4-{4-amino-2-[5-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;
- 15 3-(2-{4-amino-2-[5-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;
- 3-(2-{4-amino-2-[1-(2,3-difluoro-4-methylbenzyl)-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}thiazol-4-yl)-2,2-dimethylpropanoic acid;
- 20 3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid ;
- 3-(2-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;
- 25 (2-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)acetic acid;
- 3-(2-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-3-methylbutanoic acid;
- 30 2-(2-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)cyclopropanecarboxylic acid;

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

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

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

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

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

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

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

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

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

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

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

3-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)benzoic acid;

4-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-5-methyl-1,3-thiazol-4-yl)benzoic acid;

3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

5 3-(2-{4-amino-5-cyclopropyl-2-[5-fluoro-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}thiazol-4-yl)-2,2-dimethylpropanoic acid;

10 3-(2-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-*N*-hydroxy-2,2-dimethylpropanamide;

[5-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl]acetic acid;

15 2-[5-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl]-2-methylpropanoic acid;

(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)glycine;

20 2-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamido)-2-methylpropanoic acid;

(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)-*D*-alanine;

(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)-*L*-alanine;

25 (2*R*)-2-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamido)butanoic acid;

(2*S*)-2-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamido)butanoic acid;

30 (3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)-*D*-serine;

(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)-*D*-threonine;

N-((2*H*-tetrazol-5-yl)methyl)-3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamide;

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

3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-5-hydroxy-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-{4-[4-amino-2-(1-butyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5-{4-[2-(2*H*-tetrazol-5-yl)ethyl]phenyl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)butanoic acid;

(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)acetic acid;

4-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)butanoic acid;

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

2-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)acetic acid;

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

3-(6-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-3-yl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-cyanophenyl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-methylphenyl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-hydroxyphenyl)propanoic acid;

(5*S*)-3-{2-[4-amino-5-methyl-6-oxo-2-{1-[tetrahydro-2*H*-pyran-2-ylmethyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl}-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1,3-thiazol-4-yl}-2,2-dimethylpropanoic acid;;

3-{2-[4-amino-5-methyl-6-oxo-2-{1-[tetrahydro-2*H*-pyran-2-ylmethyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl}-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid;;

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

10 3-{2-[4-amino-5-methyl-2-{1-[4-methylcyclohexylmethyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl}-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid;

4-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-difluorobutanoic acid;

15 3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-2-yl)-2,2-dimethylpropanoic acid;

3-(6-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-3-yl)propanoic acid;

20 2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-benzothiazole-5-carboxylic acid;

3-(6-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-3-yl)-2,2-dimethylpropanoic acid;

25 3-{2-[4-amino-2-{6-chloro-1-[4-methylcyclohexylmethyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid;

(5*S*)-3-{2-[4-amino-2-{6-fluoro-1-[tetrahydro-2*H*-pyran-2-ylmethyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1,3-thiazol-4-yl}-2,2-dimethylpropanoic acid;

30 3-{2-[4-amino-2-{6-fluoro-1-[tetrahydro-2*H*-pyran-2-ylmethyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid;

4-(2-{4-amino-2-[6-fluoro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-difluorobutanoic acid;

(5*S*)-3-{2-[4-amino-2-{6-fluoro-1-[4-methylcyclohexylmethyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1,3-thiazol-4-yl}-2,2-dimethylpropanoic acid;

3-{2-[4-amino-2-{6-fluoro-1-[4-methylcyclohexylmethyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-cyclopropyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-5-cyclopropyl-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)-2,2-dimethylpropanoic acid;

2-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)-2-methylpropanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-2-yl)-2,2-dimethylpropanoic acid;

4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridine-2-carboxylic acid;

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

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

4-(2-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)benzoic acid;

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

3-(4-{4-amino-5-cyclopropyl-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

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

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

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

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

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

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

4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}benzoic acid;

4-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)benzoic acid;

(2*E*)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)prop-2-enoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-cyclopropyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(2-{4-amino-2-[6-chloro-1-(cyclohexylmethyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

(*S*)-3-(4-{4-amino-2-[6-chloro-1-(cyclopentylmethyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(2-{4-amino-2-[6-chloro-1-(cyclopentylmethyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

(*S*)-3-(2-{4-amino-2-[6-chloro-1-(cyclopentylmethyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

(*S*)-3-{4-[4-amino-2-{6-chloro-1-[(3,3-difluorocyclobutyl)methyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl}propanoic acid;

4-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)benzoic acid;

4-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)benzoic acid;

5 4-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylbutanoic acid;

4-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylbutanoic acid;

10 2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-benzoxazole-5-carboxylic acid;

3-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}benzoic acid;

15 3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-5-methyl-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-pyrazol-1-yl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-D-alanine;

20 3-(2-{4-amino-2-[6-chloro-1-(4-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

(*S*)-3-(2-{4-amino-2-[6-chloro-1-(4-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

25 3-(2-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-5-methyl-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

30 4-(2-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylbutanoic acid;

3-(2-{4-amino-2-[6-chloro-1-(2,4-difluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

(S)-3-(2-{4-amino-2-[6-chloro-1-(2,4-difluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[6-chloro-1-(2,3-difluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

5 (S)-3-(2-{4-amino-2-[6-chloro-1-(2,3-difluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[6-chloro-1-(2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

10 (S)-3-(2-{4-amino-2-[6-chloro-1-(2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

3-{2-[4-amino-2-{6-chloro-1-[(3-fluoropyridin-2-yl)methyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid;

15 (S)-3-{2-[4-amino-2-{6-chloro-1-[(3-fluoropyridin-2-yl)methyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1,3-thiazol-4-yl}-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[6-chloro-1-(3-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

20 3-(2-{4-amino-2-[6-chloro-1-(2-fluoro-3-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

(S)-3-(2-{4-amino-2-[6-chloro-1-(2-fluoro-3-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

25 3-(2-{4-amino-2-[6-chloro-1-(2,3,6-trifluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

(S)-3-(2-{4-amino-2-[6-chloro-1-(2,3,6-trifluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

30 3-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}benzoic acid;

3-(4-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-pyrazol-1-yl)-2,2-dimethylpropanoic acid;

4-(2-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylbutanoic acid;

(*S*)-3-(2-{4-amino-2-[6-fluoro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

5 3-(2-{4-amino-2-[6-fluoro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

4-(2-{4-amino-2-[6-fluoro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylbutanoic acid;

10 4-(2-{4-amino-2-[6-fluoro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylbutanoic acid;

3-(2-{4-amino-2-[6-fluoro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-5-methyl-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

15 (*S*)-3-(2-{4-amino-2-[1-(2,3-difluorobenzyl)-6-fluoro-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[1-(2,3-difluorobenzyl)-6-fluoro-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

(*S*)-3-(2-{4-amino-2-[1-(cyclohexylmethyl)-6-fluoro-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

20 3-(2-{4-amino-2-[1-(cyclohexylmethyl)-6-fluoro-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

(2-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)acetic acid;

25 4-(2-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylbutanoic acid;

4-(2-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylbutanoic acid;

30 4-{2-[4-amino-2-{6-chloro-1-[(3-fluoropyridin-2-yl)methyl]-1*H*-indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylbutanoic acid;

3-(2-{4-amino-2-[6-chloro-1-(3,3-dimethylbutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}benzoic acid;

(*S*)-3-(4-{4-amino-2-[1-(3,3-dimethylbutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

5 3-(4-{4-amino-2-[6-fluoro-1-(2-fluoro-3-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-pyrazol-1-yl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[6-fluoro-1-(2-fluoro-3-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic
10 acid;

3-(2-{4-amino-2-[6-chloro-1-(2-fluoro-5-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

(*S*)-3-(2-{4-amino-2-[6-chloro-1-(2-fluoro-5-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}1,3-thiazol-4-yl)-2,2-dimethylpropanoic
15 acid;

3-(2-{4-amino-2-[6-chloro-1-((3-fluoro-4-methylpyridin-2-yl)methyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

(*S*)-3-(2-{4-amino-2-[6-chloro-1-((3-fluoro-4-methylpyridin-2-yl)methyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

(2*E*)-3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)prop-2-enoic acid;

(2*E*)-3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)prop-2-enoic acid;

2 2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridine-4-carboxylic acid;

4-(2-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylbutanoic acid;

30 (*S*)-3-(4-{4-amino-2-[1-(4-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(*S*)-3-(2-{4-amino-2-[1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

(*S*)-3-(2-{4-amino-5-methyl-6-oxo-2-[1-(2,3,6-trifluorobenzyl)-1*H*-indazol-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

5 (*S*)-3-(4-{4-amino-5-methyl-2-[1-(3-methylbenzyl)-1*H*-indazol-3-yl]-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(2-{4-amino-5-methyl-2-[1-(3-methylbenzyl)-1*H*-indazol-3-yl]-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

10 (*S*)-3-(4-{4-amino-2-[1-(cyclopentylmethyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(2-{4-amino-2-[1-(cyclohexylmethyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

15 (*S*)-3-{2-[4-amino-5-methyl-6-oxo-2-{1-[tetrahydro-2*H*-pyran-2-ylmethyl]-1*H*-indazol-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1,3-thiazol-4-yl}-2,2-dimethylpropanoic acid;

3-{2-[4-amino-5-methyl-6-oxo-2-{1-[tetrahydro-2*H*-pyran-2-ylmethyl]-1*H*-indazol-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid;

3-{2-[4-amino-5-methyl-2-{1-[4-methylcyclohexylmethyl]-1*H*-indazol-3-yl]-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid;

20 (*S*)-3-{4-[4-amino-2-{1-[(3-fluoropyridin-2-yl)methyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl}propanoic acid;

3-(2-{4-amino-2-[1-(2-fluoro-3-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

25 (*S*)-3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-D-alanine;

3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-imidazol-4-yl)propanoic acid;

(*S*)-4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5-{4-[2-methyl-2-(2*H*-tetrazol-5-yl)propyl]thiazol-2-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 ;

(*S*)-4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-5-{4-[2-(2*H*-tetrazol-5-yl)ethyl]phenyl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(*S*)-4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5-{4-[2-methyl-2-(2*H*-tetrazol-5-yl)propyl]-1,3-thiazol-2-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5-{4-[2-methyl-2-(2*H*-tetrazol-5-yl)propyl]-1,3-oxazol-2-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 (*S*)-4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-5-{4-[2-(2*H*-tetrazol-5-yl)ethyl]phenyl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(*S*)-4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-5-{4-[2-methyl-2-(2*H*-tetrazol-5-yl)propyl]-1,3-thiazol-2-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

10 (*S*)-4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5-{4-[2-(2*H*-tetrazol-5-yl)ethyl]phenyl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5-[4-(2*H*-tetrazol-5-yl)pyridin-2-yl]-4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5-{4-[(2*H*-tetrazol-5-yl)methyl]phenyl}-4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

(*S*)-5-{4-[2-(2*H*-tetrazol-5-yl)ethyl]phenyl}-4-amino-2-{1-[(3-fluoropyridin-2-yl)methyl]-1*H*-indazol-3-yl}-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5-{5-[2-(2*H*-tetrazol-5-yl)ethyl]pyridin-2-yl}-4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 5-{5-[2-(2*H*-tetrazol-5-yl)ethyl]pyridin-2-yl}-4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5-{4-[2-methyl-2-(2*H*-tetrazol-5-yl)propyl]oxazol-2-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5-[3-(1*H*-tetrazol-5-yl)phenyl]-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

25 4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5-[4-(1*H*-tetrazol-5-yl)phenyl]-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-5-[3-(1*H*-tetrazol-5-yl)phenyl]-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

30 4-amino-5-methyl-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-[3-(2*H*-tetrazol-5-yl)phenyl]-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5-[6-(2*H*-tetrazol-5-yl)pyridin-2-yl]-4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

6-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridine-3-carboxylic acid;

6-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}picolinic acid;

5 (S)-4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5-{4-[2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)ethyl]phenyl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

[2-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)ethyl]phosphonic acid;

2-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)ethanesulfonic acid;

10 (S)-3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-*N*-(methylsulfonyl)propanamide;

(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenoxy)acetic acid;

15 3-[1-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyrrolidin-3-yl]propanoic acid;

3-(1-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}piperidin-4-yl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}cyclohexyl)propanoic acid; or a pharmaceutically acceptable salt thereof.

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

(R)-3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

25 (R)-3-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

(R)-3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

30 (R)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-bromophenyl)propanoic acid;

(5R)-3-{4-[4-amino-2-{6-chloro-1-[(4-methylcyclohexyl)methyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl}propanoic acid;

(R)-3-{4-[4-amino-2-{6-chloro-1-[tetrahydro-2*H*-pyran-2-ylmethyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

(R)-3-(4-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

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

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

10 (R)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

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

15 (R)-3-(4-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)propanoic acid;

(R)-3-(4-{4-amino-2-(1-butyl-6-chloro-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

20 (R)-3-(4-{4-amino-2-(1-butyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(R)-3-(4-{4-amino-5-methyl-6-oxo-2-[1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

25 (R)-3-(4-{4-amino-5-methyl-6-oxo-2-[1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

(5*R*)-3-(4-{4-amino-5-methyl-6-oxo-2-[1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2-methylpropanoic acid;

30 (R)-3-(4-{4-amino-2-[5-fluoro-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(R)-3-(4-{4-amino-2-[6-chloro-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(R)-3-(4-{4-amino-5-methyl-2-[6-methyl-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(R)-3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

5 (R)-3-(3-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(R)-3-(4-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

10 (R)-3-(3-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(R)-3-(4-{4-amino-2-[1-(2,3-difluoro-4-methylbenzyl)-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

15 (R)-3-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}benzoic acid;

(R)-3-(3-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

20 (R)- (4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)acetic acid;

(R)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)propanoic acid;

25 (R)-2-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)-2-methylpropanoic acid;

(R)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)-2,2-dimethylpropanoic acid;

30 (R)-1-[(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)methyl]cyclopropanecarboxylic acid;

(R)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

(5R)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2-methylpropanoic acid;

(R)-2-{4-[4-amino-2-(1-butyl-6-chloro-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1*H*-1,2,3-triazol-1-yl}acetic acid;

(R)-3-{4-[4-amino-2-(1-butyl-6-chloro-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1*H*-1,2,3-triazol-1-yl}propanoic acid;

(R)-3-{4-[4-amino-2-(1-butyl-6-chloro-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}-2,2-dimethylpropanoic acid;

(R)-3-{4-[4-amino-2-(1-butyl-6-chloro-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

(R)-3-(3-{4-amino-2-[6-chloro-1-(2-methoxyethyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

(R)-3-(4-{4-amino-2-[6-chloro-1-(2-methoxyethyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(R)-3-(4-{4-amino-2-[6-chloro-1-(4,4,4-trifluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(R)-3-(4-{4-amino-2-[6-chloro-1-(4,4,4-trifluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

(R)-3-{4-[4-amino-2-(6-chloro-1-pentyl-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

(R)-3-(4-{4-amino-2-[6-chloro-1-(cyclohexylmethyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(R)-3-{4-[4-amino-2-(6-chloro-1-hexyl-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

(R)-3-(4-{4-amino-2-[6-fluoro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(R)-3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(R)-3-(3-{4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(R)-4-(2-(4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)thiazol-4-yl)butanoic acid;

(R)-3-(2-(4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)oxazol-4-yl)propanoic acid;

5 (R)-2-(2-(4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)oxazol-4-yl)acetic acid;

(R)-3-(4-(4-amino-2-[6-chloro-1-(4,4-dimethylpentyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)phenyl)propanoic acid;

10 (R)-3-(3-(4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)phenyl)propanoic acid;

(R)-3-(2-(4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)oxazol-4-yl)propanoic acid;

(R)-4-(2-(4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)thiazol-4-yl)butanoic acid;

15 (R)-3-(2-(4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)oxazol-4-yl)-2,2-dimethylpropanoic acid;

(R)-3-(4-[4-amino-2-(6-chloro-1-[(3-fluoropyridin-2-yl)methyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl)propanoic acid;

20 (R)-3-(4-[4-amino-2-(6-chloro-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl)propanoic acid;

(R)-3-(4-(4-amino-2-[1-(2-fluorobenzyl)-6-methyl-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)phenyl)propanoic acid;

(R)-3-(4-(4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)phenyl)propanoic acid;

25 (R)-3-(3-(4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)phenyl)propanoic acid;

(R)-3-(2-(4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

30 (R)-3-(2-(4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)oxazol-4-yl)-2,2-dimethylpropanoic acid;

(R)-3-(4-(4-amino-2-[6-chloro-1-(2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)phenyl)propanoic acid;

(R)-3-(4-{4-amino-2-[6-chloro-1-(4-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(R)-3-(4-{4-amino-2-[6-chloro-1-(3-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

5 (R)-3-(4-{4-amino-2-[6-chloro-1-(4-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(R)-3-(4-{4-amino-2-[6-chloro-1-(2-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

10 (R)-3-(4-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(R)-3-(4-{2-[1-(adamantan-1-ylmethyl)-6-chloro-1*H*-indazol-3-yl]-4-amino-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(R)-3-(4-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

15 (R)-3-(2-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

(R)-3-(4-{4-amino-2-[5-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

20 (R)-3-(2-{4-amino-2-[5-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

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

25 (R)-3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid ;

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

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

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

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

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

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

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

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

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

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

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

(R)-3-(2-{4-amino-5-methyl-6-oxo-2-[1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)propanoic acid;

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

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

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

(R)-3-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

5 (R)-3-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)benzoic acid;

(R)-4-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-5-methyl-1,3-thiazol-4-yl)benzoic acid;

10 (R)-3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

(R)-3-(2-{4-amino-5-cyclopropyl-2-[5-fluoro-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}thiazol-4-yl)-2,2-dimethylpropanoic acid;

15 (R)-3-(2-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-*N*-hydroxy-2,2-dimethylpropanamide;

(R)-[5-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl]acetic acid;

20 (R)-2-[5-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl]-2-methylpropanoic acid;

(R)-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)glycine;

25 (R)-2-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamido)-2-methylpropanoic acid;

(5*R*)-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)-*D*-alanine;

30 (5*R*)-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)-*L*-alanine;

(5*R*)-(2*R*)-2-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamido)butanoic acid;

(5R)-(2S)-2-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamido)butanoic acid;

(5R)-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)-D-serine;

5 (5R)-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)-D-threonine;

(R)-*N*-((2H-tetrazol-5-yl)methyl)-3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamide;

10 (R)-3-(4-{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}-2H-1,2,3-triazol-2-yl)propanoic acid;

(R)-3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-5-hydroxy-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

15 (R)-3-{4-[4-amino-2-(1-butyl-6-methyl-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

(R)-4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5-{4-[2-(2H-tetrazol-5-yl)ethyl]phenyl}-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one;

20 (R)-4-(4-{4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)butanoic acid;

(R)-(4-{4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)acetic acid;

(R)-4-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)butanoic acid;

25 (R)-4-(4-{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}phenyl)butanoic acid;

(R)-2-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)acetic acid;

30 (R)-2-(4-{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}phenyl)acetic acid;

(R)-3-(6-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-3-yl)propanoic acid;

(R)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-cyanophenyl)propanoic acid;

(R)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-methylphenyl)propanoic acid;

5 (R)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-hydroxyphenyl)propanoic acid; or a pharmaceutically acceptable salt thereof.

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

10 (S)-3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

(S)-3-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

(S)-3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

15 (S)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-bromophenyl)propanoic acid;

(5*S*)-3-{4-[4-amino-2-{6-chloro-1-[(4-methylcyclohexyl)methyl]-1*H*-indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

20 (S)-3-{4-[4-amino-2-{6-chloro-1-[tetrahydro-2*H*-pyran-2-ylmethyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

(S)-3-(4-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

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

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

30 (S)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

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

(S)-3-(4-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)propanoic acid;

(S)-3-(4-{4-amino-2-(1-butyl-6-chloro-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(4-{4-amino-2-(1-butyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(4-{4-amino-5-methyl-6-oxo-2-[1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(4-{4-amino-5-methyl-6-oxo-2-[1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

(5*S*)-3-(4-{4-amino-5-methyl-6-oxo-2-[1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2-methylpropanoic acid;

(S)-3-(4-{4-amino-2-[5-fluoro-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(4-{4-amino-2-[6-chloro-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(4-{4-amino-5-methyl-2-[6-methyl-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(3-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(4-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(3-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(4-{4-amino-2-[1-(2,3-difluoro-4-methylbenzyl)-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}benzoic acid;

(S)-3-(3-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

5 (S)- (4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)acetic acid;

(S)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)propanoic acid;

10 (S)-2-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)-2-methylpropanoic acid;

(S)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)-2,2-dimethylpropanoic acid;

15 (S)-1-[(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)methyl]cyclopropanecarboxylic acid;

(S)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

20 (5*S*)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2-methylpropanoic acid;

(S)-2-{4-[4-amino-2-(1-butyl-6-chloro-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1*H*-1,2,3-triazol-1-yl}acetic acid;

25 (S)-3-{4-[4-amino-2-(1-butyl-6-chloro-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1*H*-1,2,3-triazol-1-yl}propanoic acid;

(S)-3-{4-[4-amino-2-(1-butyl-6-chloro-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}-2,2-dimethylpropanoic acid;

(S)-3-{4-[4-amino-2-(1-butyl-6-chloro-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

30 (S)-3-(3-{4-amino-2-[6-chloro-1-(2-methoxyethyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

(S)-3-(4-{4-amino-2-[6-chloro-1-(2-methoxyethyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(4-{4-amino-2-[6-chloro-1-(4,4,4-trifluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(4-{4-amino-2-[6-chloro-1-(4,4,4-trifluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

5 (S)-3-{4-[4-amino-2-(6-chloro-1-pentyl-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl}propanoic acid;

(S)-3-(4-{4-amino-2-[6-chloro-1-(cyclohexylmethyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

10 (S)-3-{4-[4-amino-2-(6-chloro-1-hexyl-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl}propanoic acid;

(S)-3-(4-{4-amino-2-[6-fluoro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

15 (S)-3-(3-{4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-4-(2-{4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}thiazol-4-yl)butanoic acid;

20 (S)-3-(2-{4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)propanoic acid;

(S)-2-(2-{4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)acetic acid;

(S)-3-(4-{4-amino-2-[6-chloro-1-(4,4-dimethylpentyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

25 (S)-3-(3-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)propanoic acid;

30 (S)-4-(2-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}thiazol-4-yl)butanoic acid;

(S)-3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

(S)-3-(4-[4-amino-2-{6-chloro-1-[(3-fluoropyridin-2-yl)methyl]-1*H*-indazol-3-yl}]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl)propanoic acid;

(S)-3-(4-[4-amino-2-{6-chloro-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-indazol-3-yl}]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl)propanoic acid;

5 (S)-3-(4-{4-amino-2-[1-(2-fluorobenzyl)-6-methyl-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(4-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

10 (S)-3-(3-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(2-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

(S)-3-(2-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

15 (S)-3-(4-{4-amino-2-[6-chloro-1-(2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(4-{4-amino-2-[6-chloro-1-(4-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

20 (S)-3-(4-{4-amino-2-[6-chloro-1-(3-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(4-{4-amino-2-[6-chloro-1-(4-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(4-{4-amino-2-[6-chloro-1-(2-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

25 (S)-3-(4-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(4-{2-[1-(adamantan-1-yl)methyl]-6-chloro-1*H*-indazol-3-yl]-4-amino-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

30 (S)-3-(4-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(2-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

(S)-3-(4-{4-amino-2-[5-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-(2-{4-amino-2-[5-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

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

(S)-3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid ;

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

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

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

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

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

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

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

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

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

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

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

10 (S)-3-(2-{4-amino-5-methyl-6-oxo-2-[1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)propanoic acid;

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

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

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

20 (S)-3-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

(S)-3-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)benzoic acid;

25 (S)-4-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-5-methyl-1,3-thiazol-4-yl)benzoic acid;

(S)-3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

30 (S)-3-(2-{4-amino-5-cyclopropyl-2-[5-fluoro-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}thiazol-4-yl)-2,2-dimethylpropanoic acid;

(S)-3-(2-(4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-1,3-thiazol-4-yl)-*N*-hydroxy-2,2-dimethylpropanamide;

(S)-[5-(4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl]acetic acid;

(S)-2-[5-(4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl]-2-methylpropanoic acid;

(S)-(3-(4-(4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)glycine;

(S)-2-(3-(4-(4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamido)-2-methylpropanoic acid;

(5*S*)-(3-(4-(4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)-D-alanine;

(5*S*)-(3-(4-(4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)-L-alanine;

(5*S*)-(2*R*)-2-(3-(4-(4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamido)butanoic acid;

(5*S*)-(2*S*)-2-(3-(4-(4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamido)butanoic acid;

(5*S*)-(3-(4-(4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)-D-serine;

(5*S*)-(3-(4-(4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)-D-threonine;

(S)-*N*-((2*H*-tetrazol-5-yl)methyl)-3-(4-(4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamide;

(S)-3-(4-(4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)-2*H*-1,2,3-triazol-2-yl)propanoic acid;

(S)-3-(4-(4-amino-2-[6-chloro-1-(2-fluorobenzyl)-5-hydroxy-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

(S)-3-{4-[4-amino-2-(1-butyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

(S)-4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5-{4-[2-(2*H*-tetrazol-5-yl)ethyl]phenyl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

5 (S)-4-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)butanoic acid;

(S)-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)acetic acid;

10 (S)-4-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)butanoic acid;

(S)-4-(4-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)butanoic acid;

(S)-2-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)acetic acid;

15 (S)-2-(4-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)acetic acid;

(S)-3-(6-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-3-yl)propanoic acid;

20 (S)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-cyanophenyl)propanoic acid;

(S)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-methylphenyl)propanoic acid;

25 (S)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-hydroxyphenyl)propanoic acid; 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. Reference to the compounds of structural Formula (I) includes the compounds of other generic structural Formulas and embodiments that fall within
30 the scope of Formula (I), including but not limited to the compounds of Formulas (IA) or (IB).

"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.

5 "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
10 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.

15 "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,
20 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
25 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 and bicyclic ring structures in which one or more atoms in the ring, the heteroatom(s), is an element other than carbon. Heteroatoms are
30 typically O, S, or N atoms. Examples of heteroaromatic groups include: pyridinyl, pyrimidinyl, pyrrolyl, pyridazinyl, isoxazolyl, thiazolyl, oxazolyl, indolyl, benzoxazolyl, benzothiazolyl, 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.*, R¹, R², etc.) 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.*, R¹, R², 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 R¹ 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
5 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. Where a structural formula of the compounds of Formula (I) indicates a straight line at
10 a chiral center, the structural formula includes both the S and R stereoisomers associated with the chiral center and mixtures thereof.

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
15 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. Vibrational circular dichroism (VCD) may also be used to determine the absolute stereochemistry. Alternatively, any stereoisomer or isomers of a compound of Formula (I) may be obtained by stereospecific
20 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
25 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
30 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 with compounds of Formulas I of the present invention.

5 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
10 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
15 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
20 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
25 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'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-
30 morpholine, 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. 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.

The activity of the compounds *in vivo* can be assessed in various animal models of hypertension, such as by measuring their acute efficacy in spontaneously hypertensive rats (SHR). In addition, the activity of the compounds can be assessed by measuring the pulmonary and systolic blood pressure in a hypoxia-induced pulmonary hypertension rat model following intratracheal administration of sGC stimulator compounds. In one embodiment, preferred compounds of the Formula (I) achieve a minimum decrease in pulmonary arterial pressure of ≥ 15 mmHg for the corresponding smaller decrease in systolic blood pressure in the hypoxia-induced pulmonary hypertension rat model. For instance, in one embodiment, preferred compounds of the Formula (I) achieve a minimum decrease in pulmonary arterial pressure of ≥ 15 mmHg for the corresponding decrease in systolic blood pressure, which decrease is ≤ 10

mmHg in this assay. The Biological Assays section below describes these *in vivo* models of hypertension.

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. In a preferred embodiment, the term "therapeutically effective amount" means an amount of a pharmaceutical drug that alleviates at least one clinical symptom in a human patient. The terms "prophylactically effective (or efficacious) amount" and similar 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 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 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 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, pulmonary hypertension (WHO Groups 1-5), which includes pulmonary arterial hypertension (PAH), stable and unstable angina pectoris, thromboses, restenoses, myocardial infarction, strokes, cardiac insufficiency, fibrosis or pulmonary hypertonia, or, for example, erectile dysfunction, asthma (*e.g.*, bronchial asthma) , 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, and diabetes. Compounds of Formula (I) can additionally be used in the therapy of cirrhosis of the liver and also for improving a restricted memory performance or ability to learn.

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, diabetic retinopathy, cirrhosis of the liver, chronic obstructive pulmonary disease (COPD), acute respiratory distress
10 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 pharmaceutical compositions. The term "patient" includes animals, preferably mammals and especially humans, who use the instant
15 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 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
20 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 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
25 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 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,
30 *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,
5 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.

10 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.

15 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
20 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-

25 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.
30 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 0.01 to 200 mg, such as 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. In some embodiments, the amount of active compound of Formula (I) and/or its pharmaceutically acceptable salts in the pharmaceutical composition is from 0.01 to 10 mg per dose. 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 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 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 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 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 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, or on whether other active compounds are administered in addition to compounds of Formula (I). In general, a daily dose of approximately 0.0001 to 100 mg/kg, in particular, 0.0001 to 0.30 mg/kg or 0.01 to 0.03 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.

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
5 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, 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
10 to mean a pharmaceutically active agent (or agents) that is active in the body, 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
15 as a lipid modifying compound, anti-diabetic agents and/or anti-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
20 employed include but are not limited to 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
25 such as HYZAAR®); 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.
30 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 pyroliimidazolones (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 Glumetza™, Fortamet™, and GlucophageXR™; 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, evacetrapib, and torcetrapib); 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

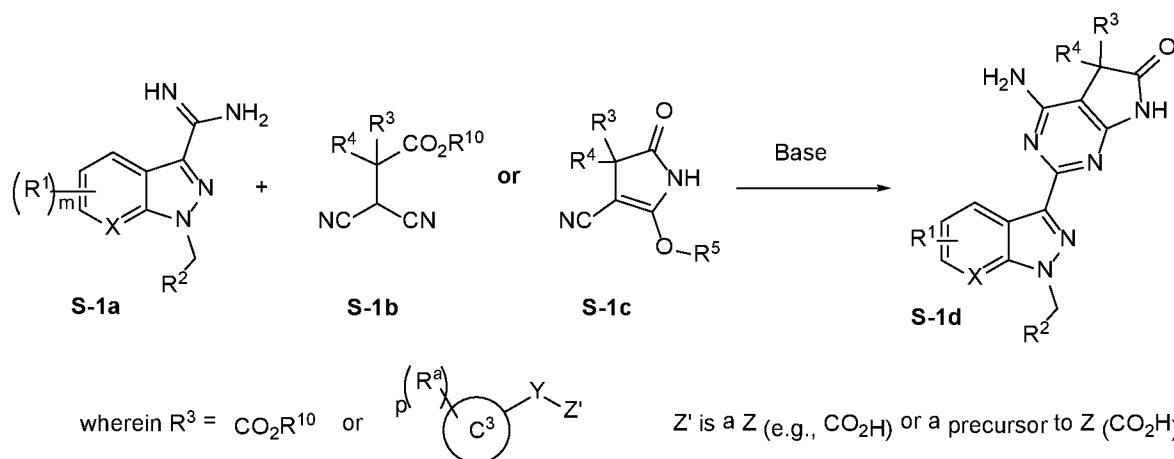
WO 2009/000087); SGLT inhibitors (*e.g.*, ASP1941, SGLT-3, empagliflozin, dapagliflozin, ertugliflozin, canagliflozin, BI-10773, PF-04971729, remogliflozin, TS-071, tofogliflozin, ipragliflozin, and LX-4211); inhibitors of acyl coenzyme A:diacylglycerol acyltransferase 1 and 2 (DGAT-1 and DGAT-2); inhibitors 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, and pharmaceutically acceptable salt forms of the above active agents where chemically possible.

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" and "X" groups in the Schemes correspond to the variables defined in Formula (I) at the same positions on the structures.

Scheme 1 outlines the general approach to assembling compounds of type **S-1d**. Starting with an amidine **S-1a** and coupling with either malononitrile **S-1b** or lactam **S-1c**, in the presence of either an inorganic base (*e.g.*, KHCO_3) or amine base (*e.g.*, NEt_3) respectively, affords pyrimidine containing substrates **S-1d**.

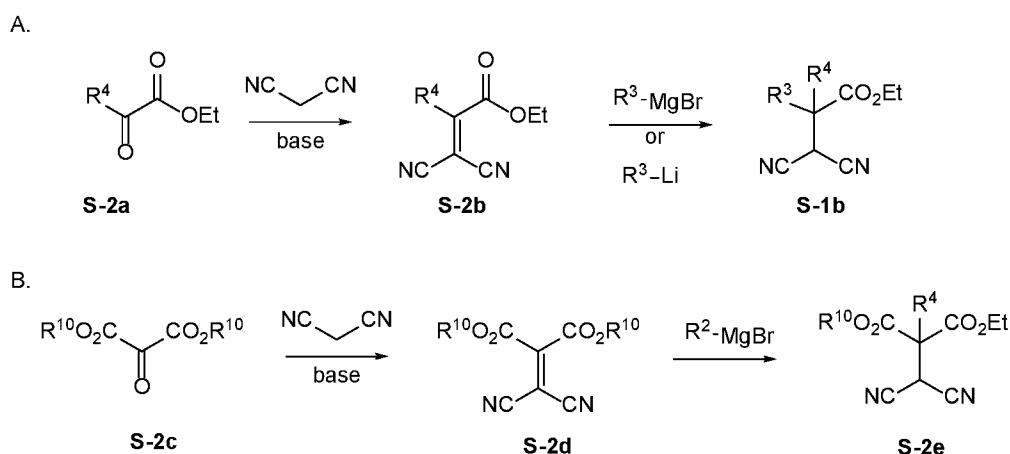
Scheme 1



Malononitrile type coupling partners can be assembled as outlined in **Scheme 2**, lines A and B. Intermediate **S-2a** can either be purchased ($R^4 = \text{Me}$), or can be generated in one-step from diethyl oxalate through treatment with a Grignard reagent or other organometallic reagents.

- 5 Condensation of malononitrile with intermediate **S-2a**, analogous to literature conditions (Hagiwara et. al. *Synthesis* **1974**, 9, 669) affords intermediate **S-2b**. Subsequent 1,4-addition with a Grignard reagent or lithiate in a solvent such as THF at room temperature to -78°C affords functionalized malononitrile **S-1b**. An alternate approach to derivatized malononitriles, in which the R^4 group is introduced later, is outlined in line B. Starting with a di-alkyl oxalate, condensation with malononitrile analogous to conditions described in the literature (Sentman et. al. *J. Org. Chem.* **1982**, 47, 4577) affords intermediate **S-2d**. Subsequent treatment with an
- 10 Grignard reagent affords intermediate **S-2e**, analogous to intermediate **S-1b** when $R^3 = \text{CO}_2R^{10}$.

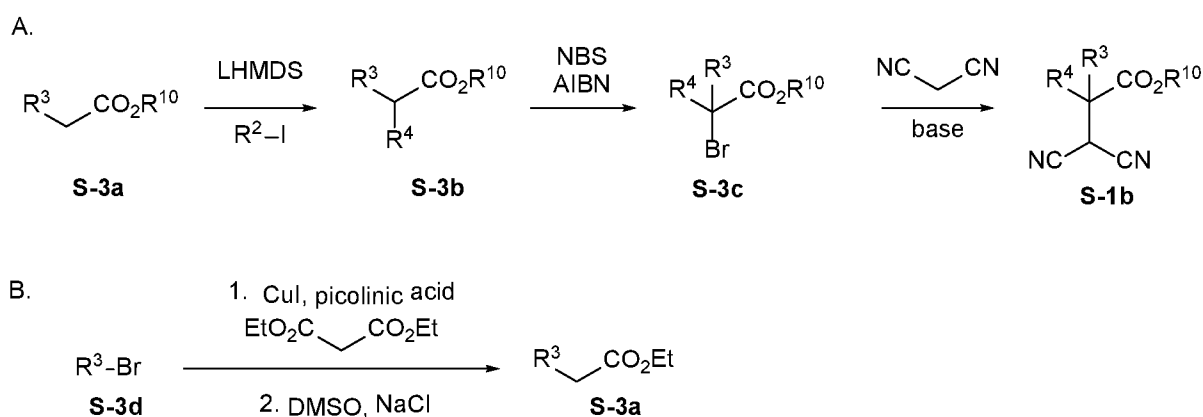
Scheme 2



- 15 An alternative method for assembling malononitrile type reagents is outlined below in **Scheme 3**. Functionalized esters **S-3a** can either be purchased or assembled via copper catalyzed cross-coupling reactions followed by decarboxylation as outlined in line B of **Scheme 3**. **S-3a** may also be prepared from the corresponding carboxylic acid by treatment with trimethylsilyl

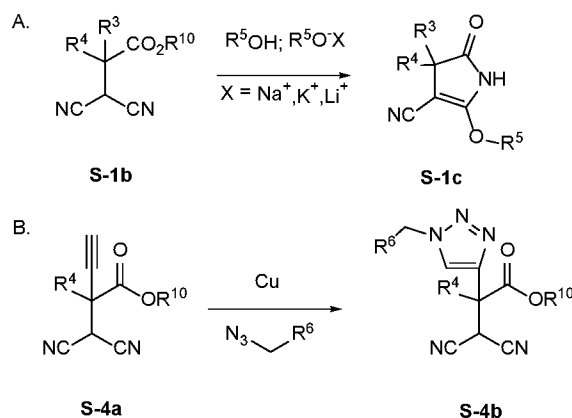
diazomethane or methanol with catalytic sulfuric acid. **S-3a** may be prepared by the alpha arylation/heteroarylation of esters as described by Buchwald, S. L. et al *Organic Letters* **2009**, 11(8), 1773; or by Shen, H. C. et al *Organic Letters* **2006**, 8(7), 1447. Additional functionalization of **S-3a** via alkylation in the presence of a base such as LiHMDS, NaHMDS, NaH or LDA in a solvent such as THF or DMF affords intermediate **S-3b**. The compound **S-3c** is prepared by treating compound **S-3b** with a brominating reagent such as NBS and AIBN in a solvent such as carbon tetrachloride at refluxing temperatures. Alternatively, the compound **S-3c** may be prepared by reaction with NBS and magnesium perchlorate in acetonitrile solvent at room temperature as described by Yang, D. et al *Journal of Organic Chemistry* **2002**, 67(21), 7429. Compound **S-3c** may also be prepared by treating compound **S-3b** with a base such as sodium hydride followed by treatment with NBS. Compound **S-1b** is obtained from **S-3c** by reaction with malononitrile and a base such as sodium hydride, t-BuOK, K₂CO₃ or DBU in a solvent such as THF or DMF at ambient temperature to elevated temperatures.

Scheme 3

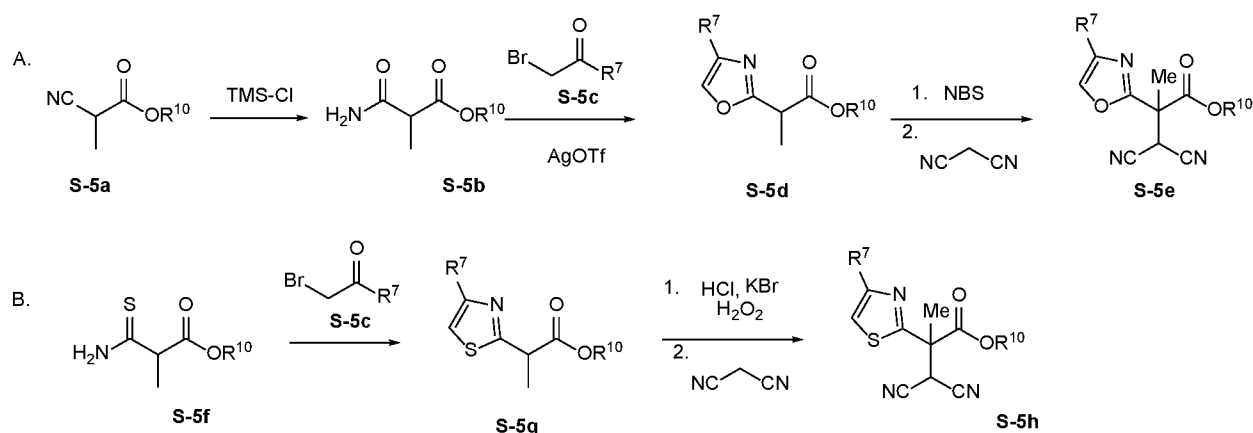


Malononitriles of type **S-1b** can be cyclized in the presence of alkoxide type bases such as sodium methoxide in methanol or sodium ethoxide in ethanol to form lactams **S-1c** as shown in **Scheme 4**. Additionally, functionalized alkyne containing malononitrile **S-4a** can undergo 1,3-dipolar cycloaddition with functionalized carbon-linked azides in the presence of a copper reagent to afford 1,2,3-triazoles **S-4b**.

Scheme 4



Heterocycles of type **S-5e** and **S-5h** can be generated as outlined in **Scheme 5**, lines A and B. **S-5e** can be prepared as outlined in line A starting from commercially available ethyl 2-cyanopropanoate **S-5a**, in which treatment with chlorotrimethyl silane in water affords amide **S-5b**. Subsequent cyclization with a functionalized α -bromoketone reagent such as **S-5c** in the presence of silver triflate leads to **S-5d**. From here, bromination with NBS and LiHMDS, followed by treatment with malononitrile, affords target substrates such as **S-5e**. **S-5h** can be accessed as outlined in line B, starting from commercially available thioamide **S-5f**. Treatment with α -bromoketones such as **S-5c**, followed by bromination with KBr and hydrogen peroxide and followed lastly by treatment with malononitrile affords substrates of type **S-5h**.

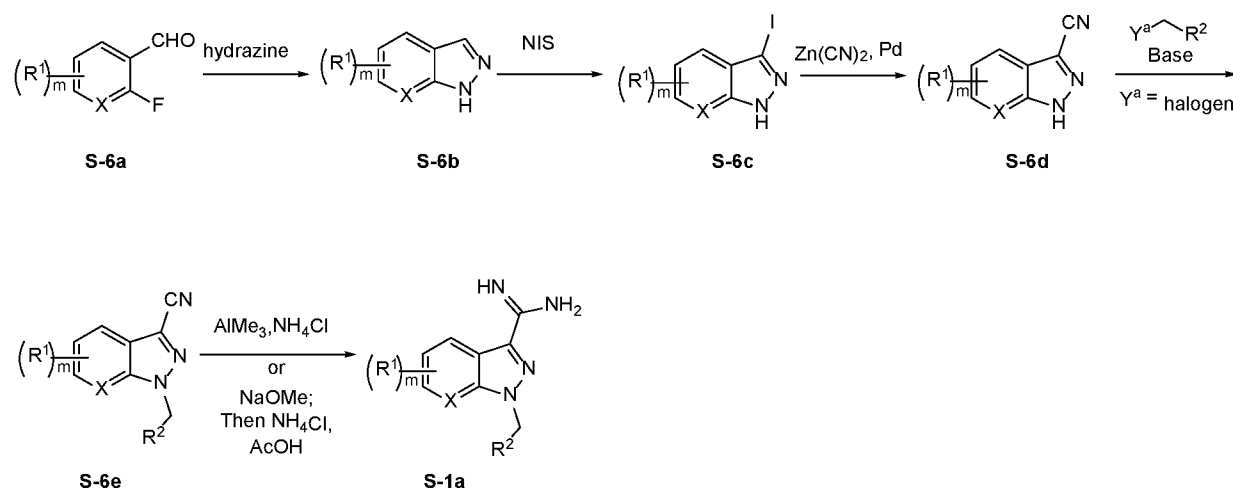
Scheme 5

The general approach to amidines **S-1a** is outlined in **Scheme 6** below. Starting with generic type 2-fluorobenzaldehyde **S-6a**, condensation with hydrazine while heating in a solvent such as DMA affords the indazole **S-6b**. Subsequent iodination with an iodination reagent such as NIS in a solvent such as DCM or DMA, followed by palladium catalyzed cross coupling with zinc cyanide using a catalyst such as $\text{Pd}_2(\text{dba})_3$ and DPPF in a solvent such as DMA affords the nitrile intermediate **S-6d**. Alkylation of the indazole with bromo or iodo halide using a base such

as cesium carbonate, sodium hydride or K_2CO_3 in a solvent such as DMF, DMA or acetonitrile at ambient temperature to 100 °C gives **S-6e**. Conversion of the nitrile to amidines of type **S-1a** can be accomplished with a reagent such as amino(chloro)methylaluminum, prepared from trimethylaluminum and ammonium chloride, in a non-polar solvent such as toluene while

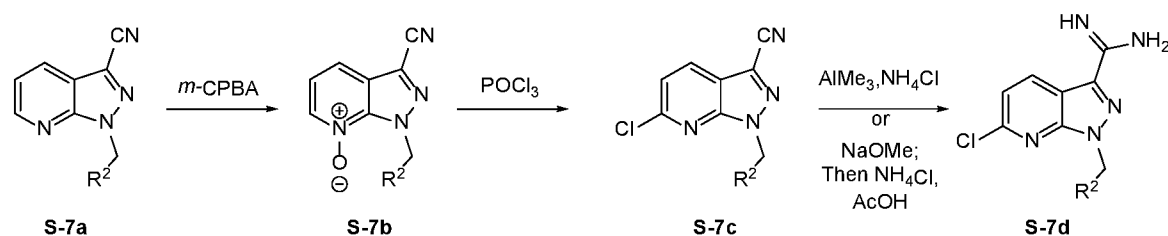
heating as described by Garigipati, R. S. *et al. Tetrahedron Letters* **1990**, 31(14), 1969. Alternative conditions utilize sodium methoxide followed by treatment with ammonium chloride in the presence of acetic acid.

Scheme 6



As described in **Scheme 7**, aza-indazole substrates **S-7a** can be further functionalized by oxidation of the pyridine with *m*CPBA in acetic acid solvent to afford the *N*-oxide, followed by treatment with $POCl_3$ to afford the alpha-chloro substituted intermediate **S-7c** that can be subsequently converted to amidine **S-7d**.

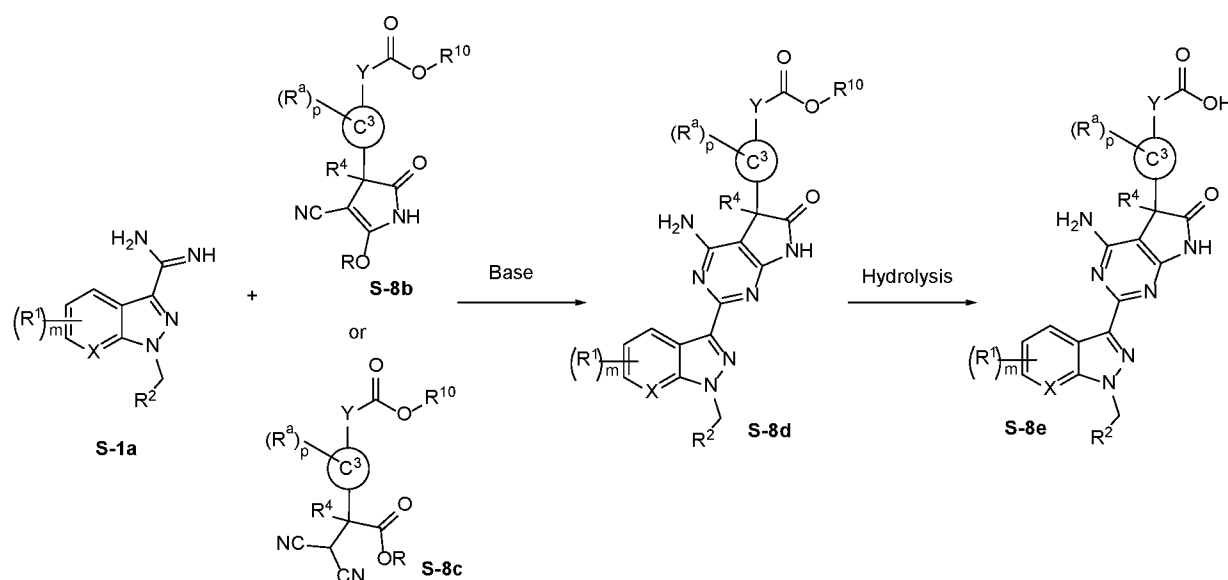
Scheme 7



Some common routes for final compound synthesis are outlined in the **Schemes 8, 9** and **10** below. One approach as generically outlined in **Scheme 8**, is coupling of functionalized malononitrile **S-8c** or lactam **S-8b** with amidines to afford intermediates of type **S-8d** bearing an ester. Amidine coupling with malononitrile reagents of type **S-8c**, typically are performed in an alcohol solvent such as *t*BuOH at RT to 80 °C and utilize a base such as $KHCO_3$, though reactions can also be run in the absence of base. Amidine couplings with activated lactam

structures such as **S-8b** are typically ran in solvents such as THF at room temperature to 80 °C with an alkyl amine base such as Et₃N. Subsequent hydrolysis with a base such as lithium hydroxide in a solvent mixture containing a polar organic solvent such as dioxane or acetonitrile in combination with water affords final products **S-8e**. Chiral resolution of enantiomers can occur at any of the stages up to and including post hydrolysis formation of **S-8e**. This resolution includes chiral resolution of functionalized malonitriles **S-8c** or lactams **S-8b** or post condensation with amidines at the ester intermediate **S-8d** or post hydrolysis resolution of acid **S-8e**.

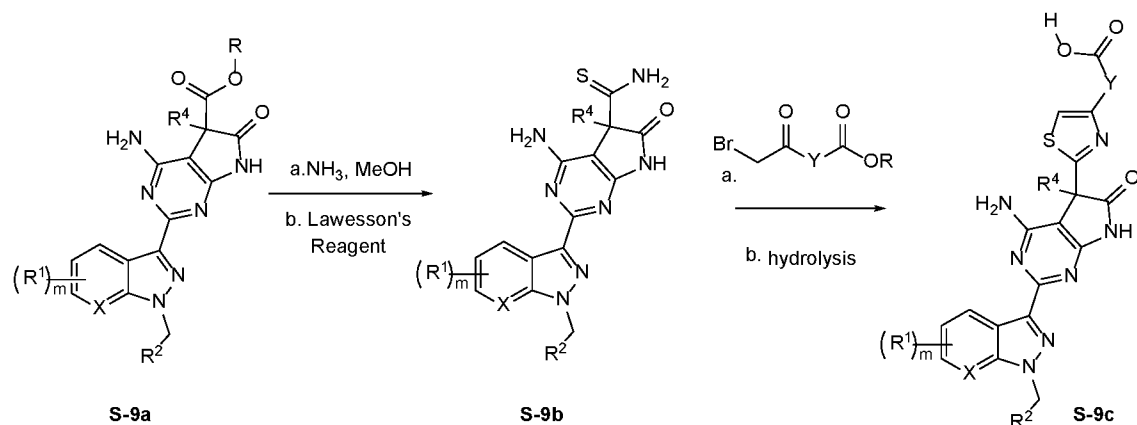
Scheme 8



Another method for the synthesis of functionalized acids linked to thiazoles is outlined in **Scheme 9**. Starting from either chiral or racemic **S-9a** (assembled as generally outlined in Scheme 1), conversion to the amide with ammonia in methanol, followed by treatment with Lawesson's reagent in toluene at elevated temperatures affords thioamide intermediate **S-9b**.

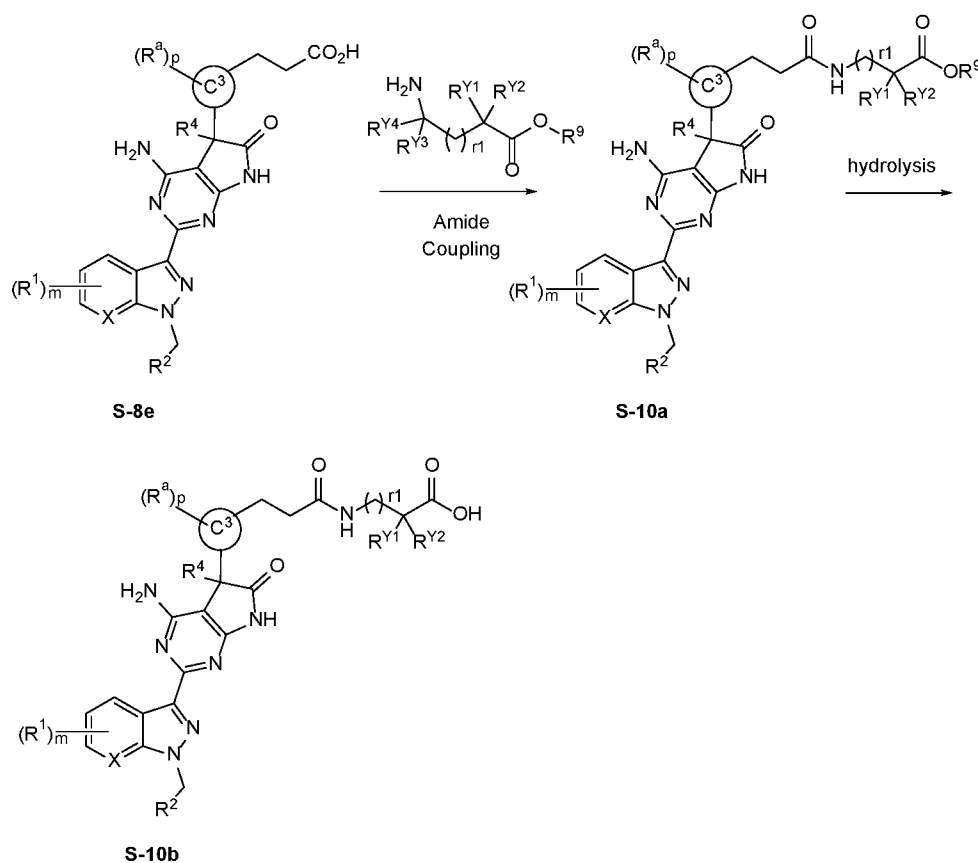
Coupling with bromo-functionalized β -keto esters in an alcohol such as ethanol at elevated temperatures followed by hydrolysis affords acid **S-9c**. In addition to generating chiral **S-9a** through use of chiral reagents of type **S-1c** or resolution of ester **S-9a**, chiral resolution can occur at thioamide **S-9b** or the subsequent ester or acid **S-9c**.

Scheme 9



Additionally, compounds of type **S-10b** can be formed from the more active single enantiomers of type **S-8e** (general synthesis outlined in **Scheme 8**) using common coupling reagents such as *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate to couple with amino-esters. The ester intermediate **S-10a** can then be hydrolyzed to provide **S-10b**.

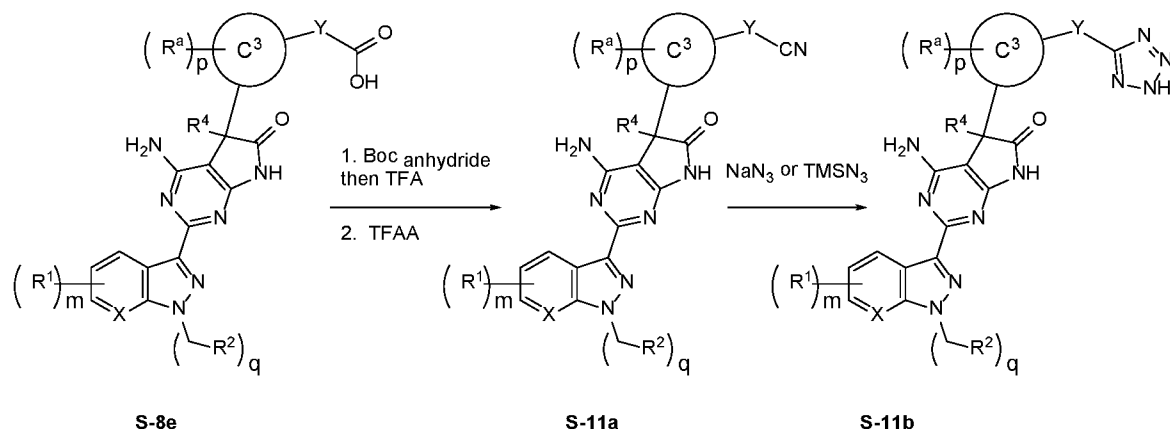
Scheme 10



Compounds of type **S-11b** can be formed from type **S-8e** (general synthesis outlined in **Scheme 8**). The nitrile compounds **S-11a** can be formed by conversion of the carboxylic acid to the corresponding amide using reagent such as Boc anhydride and TFA, followed by dehydration of the amide to form the nitrile with reagents such as trifluoroacetic anhydride.

Treatment of compounds of type **S-11a** with sodium azide or TMS-azide provides tetrazole compounds type **S-11b**.

Scheme 11



Compounds of the present invention possess an asymmetric center at the carbon bearing the R^3 and R^4 substituents which can be either 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 as outlined in **Schemes 8, 9 and 10**. For example, intermediates **S-1b** and **S-1c** can undergo chiral resolution to afford enantiopure isomers that may be carried on in the coupling with amidines to enantiomerically pure compounds. Alternatively, enantiomeric resolution can be performed post formation of general intermediate **S-1d**. For example, chiral resolution of intermediates of the type **S-8d**, **S-9b**, or **S-10a** to single enantiomers may be further elaborated to enantiopure compounds or may be resolved at final compounds of type **S-8e**, **S-9c**, **S-10b**. 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; atm = atmosphere; bp, b.p. = boiling point; br s = broad singlet; 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 =

5 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; dppf = 1,1'-bis(diphenylphosphino)ferrocene; DTT = dithiothreitol;

10 EAB = egg albumin; EBSS = Earle's balanced salt solution; equiv, eq. = equivalent(s); Et = ethyl; Et₃N = triethylamine; EtOAc = ethyl acetate; EtOH = ethanol; GTP = guanosine triphosphate; h, hr = hour; HPLC = High pressure liquid chromatography; Int. = intermediate; *i*Pr = isopropyl; IPA, IP = inflection points; *i*-PrOH = Isopropanol; IT = intra-tracheal; LCMS, LC/MS = liquid chromatography-mass spectrometry; LDA = lithium diisopropylamide;

15 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; NMR = nuclear magnetic resonance; N.D. = not determined; NIS = *N*-iodo succinimide; PDA = photodiode array; Pd₂(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; TFA = trifluoroacetic acid; TFAA =

20 trifluoroacetic anhydride; TLC = thin layer chromatography; THF = tetrahydrofuran; TMS = trimethylsilyl; 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 =

30 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 or ambient temperature (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 nitrogen 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 was 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. When line-listed, NMR data are in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to residual solvent peaks (multiplicity and number of hydrogens). 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/acetonitrile (0.1% TFA) gradient (typically 5% acetonitrile to 95% acetonitrile) or using a SUNFIRE Prep C18 OBD 5µM column (100 x 30 mm i.d.) eluting at 50 mL/min with a water/acetonitrile (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 (hours), 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).

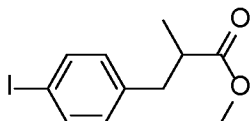
The following are representative procedures for the preparation of intermediates used to prepare the final products described in the Examples that follow thereafter. These examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

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 **37 (I-37, or rac I-37)**, and the separated stereoisomers are noted as Intermediates **37A** and **37B** (or **I-37A** and **I-37B**). 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-11B**. 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 separation. In such cases, the intermediate or example number can be followed by 2 letters (*e.g.* I-38AB or Ex-5BA). 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.

INTERMEDIATE 1

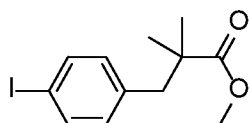
Methyl 3-(4-iodophenyl)-2-methylpropanoate



To a flask under an inert atmosphere of nitrogen, containing a solution of methyl 3-(4-iodophenyl)propanoate (2 g, 6.89 mmol) in 27 mL THF at -78°C was slowly added a solution of potassium bis(trimethylsilyl)amide (1 M in THF, 8.3 mL, 8.3 mmol). The resulting solution was stirred 30 min at -78°C before methyl iodide (0.560 mL, 8.96 mmol) was added. The reaction was stirred 2 h at -78°C then quenched with a 1 M aq. solution of hydrochloric acid. The mixture was extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. MgSO_4 , filtered and concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using an EtOAc:hexane gradient to afford the racemic title product **I-1**. ^1H NMR (500 MHz, CDCl_3) δ 7.66 – 7.60 (m, 2H), 6.94 (d, $J = 8.2$ Hz, 2H), 3.67 (s, 3H), 2.99 (dd, $J = 13.5, 7.1$ Hz, 1H), 2.73 (h, $J = 7.0$ Hz, 1H), 2.64 (dd, $J = 13.4, 7.4$ Hz, 1H), 1.18 (d, $J = 6.9$ Hz, 3H); $m/z = 305$ ($\text{M}+1$).

INTERMEDIATE 2

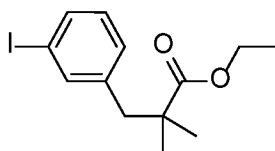
Methyl 3-(4-iodophenyl)-2,2-dimethylpropanoate



To a flask under an inert atmosphere of nitrogen, containing a solution of methyl isobutyrate (1.16 mL, 10.1 mmol) in THF (34 mL) at -78°C was slowly added a solution of lithium diisopropylamide (1 M in THF, 11.1 mL, 11.1 mmol). The resulting solution was stirred 1 h at -78°C before a solution of 4-iodobenzyl bromide (3 g, 10.10 mmol) in THF (2 mL) was added. The reaction was allowed to warm up to RT and stirred 2 h, then quenched by the addition of sat. aq. NH_4Cl . The mixture was extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. MgSO_4 , filtered and concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using an EtOAc:hexane gradient to afford the racemic title product **I-2**. ^1H NMR (500 MHz, CDCl_3) δ 7.65 – 7.54 (m, 2H), 6.94 – 6.81 (m, 2H), 3.68 (s, 3H), 2.82 (s, 2H), 1.20 (s, 6H); $m/z = 319$ ($\text{M}+1$).

INTERMEDIATE 3

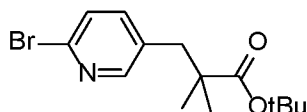
Ethyl 3-(3-iodophenyl)-2,2-dimethylpropanoate



The title compound **I-3** was prepared using essentially the same procedures described for intermediate **2** using 3-iodobenzyl bromide and ethyl isobutyrate as starting material. $m/z = 333$ (M+1)

INTERMEDIATE 4

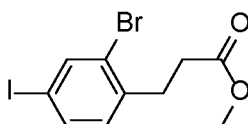
5 **Tert-butyl 3-(6-bromopyridin-3-yl)-2,2-dimethylpropanoate**



The title compound **I-4** was prepared using essentially the same procedures described for intermediate **2** using 2-bromo-5-(bromomethyl)pyridine and *t*-butyl isobutyrate as starting material. $m/z = 316$ (M+1)

INTERMEDIATE 5

10 **Methyl 3-(2-bromo-4-iodophenyl)propanoate**



Step A- 3-(2-bromo-4-nitrophenyl)propanoic acid. To a flask containing 3-(4-nitrophenyl)propanoic acid (8 g, 41.0 mmol) in water (40 mL) and concentrated sulfuric acid (40 mL) at 0 °C was slowly added *N*-bromosuccinimide (9.48 g, 53.3 mmol). The resulting mixture was stirred in the dark for 2 h at 40 °C, then diluted with water and extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo* to dryness to afford the title compound.

Step B- methyl 3-(2-bromo-4-nitrophenyl)propanoate. Into a flask were placed 3-(2-bromo-4-nitrophenyl)propanoic acid (16 g, 40.9 mmol) concentrated sulfuric acid (20 mL) and MeOH (40 mL). The resulting mixture was stirred for 2 h at 80 °C then cooled to RT, diluted with water and extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography with EtOAc:petroleum ether (0-30%) to afford the title compound.

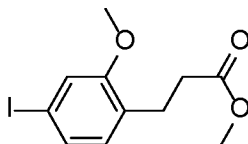
Step C- methyl 3-(4-amino-2-bromophenyl)propanoate. Into a flask were placed methyl 3-(2-bromo-4-nitrophenyl)propanoate (10.0 g, 24.3 mmol), iron (5.4 g, 97 mmol) and ammonium chloride (3.9 g, 72.9 mmol) in a mixture of ethanol (80 mL) and water (20 mL). The resulting mixture was stirred for 1 h at 90 °C. The solid was filtered out, and washed with EtOAc. The organic layer was washed with brine, dried over anhydr. Na₂SO₄, and filtered. The filtrate was

concentrated *in vacuo* and the residue was dissolved in water, the pH of the solution was adjusted to pH 1 with hydrochloric acid (1 N). The resulting solution was extracted with EtOAc (2 X). The pH adjusted to 10 with sodium hydroxide (1 N). The resulting solution was extracted with EtOAc (3 X) and the organic layer combined, dried over anhydr. Na₂SO₄, filtered and the filtrate was concentrated *in vacuo* to dryness to afford the title compound.

Step D- methyl 3-(2-bromo-4-iodophenyl)propanoate. To a flask containing methyl 3-(4-amino-2-bromophenyl)propanoate (5.0 g, 19.4 mmol), concentrated hydrochloric acid (15 mL) and water (13 mL) at 0 °C was added dropwise a solution of sodium nitrite (1.47 g, 21.3 mmol) in water (2 mL). The mixture was stirred for 1 h at 0 °C before potassium iodide (6.43 g, 38.7 mmol) was added. After an additional 5 min at 0 °C the mixture was diluted with Et₂O and washed with of aq. sat. NaHSO₄. The organic layer was dried over anhydr. MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc:petroleum ether (0-30%) to afford the title compound **I-5**. ¹H NMR (300 MHz, CDCl₃) δ 7.85 (d, *J* = 1.8 Hz, 1H), 7.51 (dd, *J* = 1.8, 8.4 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 3.65 (s, 3H), 2.98 (t, *J* = 7.5 Hz, 2H), 2.60 (t, *J* = 7.5 Hz, 2H).

INTERMEDIATE 6

Methyl 3-(4-iodo-2-methoxyphenyl)propanoate



Step A- 7-iodochroman-2-one. Into a flask were placed 3-(4-iodophenyl)propanoic acid (6.0 g, 21.7 mmol), trifluoroacetic acid (109 mL) and [bis(trifluoroacetoxy)iodo]benzene (14.0 g, 32.6 mmol). The mixture was cooled to 0 °C and of boron trifluoride etherate (4.1 mL, 32.6 mmol) was added dropwise. The resulting mixture was stirred for 16 h at RT. The reaction was quenched by the addition of aq. sat. NaHCO₂, extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo*. and the residue was purified by silica gel column chromatography with EtOAc:petroleum ether (0-30%) to afford the title compound.

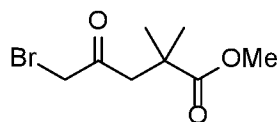
Step B- 3-(2-hydroxy-4-iodophenyl)propanoic acid. Into a flask containing 7-iodochroman-2-one (2.8 g, 10.2 mmol) in a THF (20 mL) water (20 mL) mixture was added LiOH (2.1 g, 51.1 mmol). The resulting mixture was stirred for 16 h at RT. The reaction was quenched by the addition of aq. solution of hydrochloric acid (2 N) extracted with EtOAc (3X). The organic layer

was washed with brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo* to dryness to afford the title compound.

Step C- methyl 3-(4-iodo-2-methoxyphenyl)propanoate. Into a flask containing 3-(2-hydroxy-4-iodophenyl)propanoic acid (3.0 g, 10.3 mmol) and iodomethane (1.9 mL, 30.8 mmol) in DMF (50 mL) was added potassium carbonate (5.7 g, 41.1 mmol). The resulting mixture was stirred for 16 h at 50 °C. The reaction was quenched by the addition of water extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc:petroleum ether (0-30%) to afford the title compound **I-6**. ^1H NMR (300 MHz, CDCl_3): δ 7.49 (dd, J = 8.7 Hz, 2.4 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 6.61 (d, J = 8.7 Hz, 1H), 3.81 (s, 3H), 3.69 (s, 3H), 2.88 (t, J = 7.5 Hz, 2H), 2.59 (t, J = 7.5 Hz, 2H).

INTERMEDIATE 7

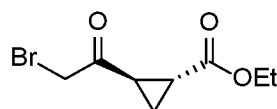
Methyl 5-bromo-2,2-dimethyl-4-oxopentanoate



To a flask containing methyl 4-chloro-2,2-dimethylpent-4-enoate (19.0 mL, 113 mmol) in a ethanol (100 mL) water (75 mL) mixture at 0 °C was added dropwise bromine (5.95 mL, 115 mmol) and the reaction was stirred 3 h at 0 °C. The reaction was diluted with water extracted with DCM (3X). The organic layers were combined washed with aq. sat. NaHCO_3 (2X) and Brine (1X), dried over anhydr. MgSO_4 , and filtered. The filtrate was concentrated *in vacuo* to dryness to afford the title compound **I-7**. ^1H NMR (500 MHz, CDCl_3): δ 3.86 (s, 2H); 3.67 (s, 3H); 2.93 (s, 2H); 1.26 (s, 6H).

INTERMEDIATE 8

Trans-ethyl 2-(2-bromoacetyl)cyclopropane-1-carboxylate

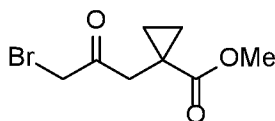


To a flask containing *trans*-ethyl 2-acetylcyclopropanecarboxylate (700 mg, 4.48 mmol) in ethanol (14 mL) at 0 °C was added dropwise bromine (0.28 mL, 5.38 mmol). The resulting mixture was stirred for 3 h at 0 °C and 16 h at RT. The reaction solution was quenched by the addition of water, extracted with DCM. The organic layers combined, washed with aq. sat. NaHCO_3 and brine, dried over anhydr. MgSO_4 , and filtered. The filtrate was concentrated *in*

vacuo to dryness to afford the title product. ^1H NMR (300 MHz, CDCl_3) δ 4.22-4.09 (m, 2H), 4.05 (s, 2H), 2.75-2.68 (m, 1H), 2.29-2.23 (m, 1H), 1.59-1.48 (m, 2H), 1.32-1.26 (m, 3H).

INTERMEDIATE 9

Methyl 1-(3-bromo-2-oxopropyl)cyclopropane-1-carboxylate



Step A- *tert*-butyl 1-(2-(bromomethyl)allyl)cyclopropane-1-carboxylate

To a flask, under an inert atmosphere of nitrogen, containing diisopropylamine (8.90 g, 88 mmol) in THF (75 mL) at -78°C was added dropwise *n*-butyllithium (32.3 mL, 81 mmol, 2.5M in THF). The resulting mixture was slowly warmed to RT and stirred for 30 min at RT then cool back down to -78°C . *tert*-butyl cyclopropanecarboxylate (10 g, 70.3 mmol) was added dropwise and the resulting mixture was stirred for 3 h at -78°C before 2,3-dibromoprop-1-ene (15.5 g, 77 mmol) was added dropwise. The resulting mixture was slowly warmed up to RT and stirred for 16 h at RT. The reaction was quenched by the addition of aq. sat. NH_4Cl , extracted with EtOAc (3X). The organic layers were combined, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc: petroleum ether (0-10%) to afford the title compound.

Step B- 1-(3-bromo-2-oxopropyl)cyclopropane-1-carboxylic acid

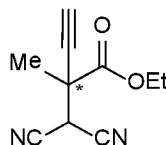
To a flask containing *tert*-butyl 1-(2-(bromomethyl)allyl)cyclopropane-1-carboxylate (1.0 g, 3.83 mmol) in a ethanol (5 mL), and water (4 mL) mixture at 0°C was added bromine (673 mg, 4.21 mmol). The resulting mixture was stirred for 4 h at RT then concentrated *in vacuo* to afford the crude title material that was used directly in step C.

Step C- methyl 1-(3-bromo-2-oxopropyl)cyclopropane-1-carboxylate

To a flask containing crude 1-(3-bromo-2-oxopropyl)cyclopropane-1-carboxylic acid (assumed 3.83 mmol) in MeOH (10 mL) was added sulfuric acid (0.5 mL, 9.38 mmol) and the resulting mixture was stirred for 2 h at reflux. The reaction mixture was cooled to RT, diluted with EtOAc washed with aq. sat. NaHCO_3 (2 X) and brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc: petroleum ether (5-15%) to afford **I-9**. ^1H NMR (400 MHz, CDCl_3) δ 4.00 (s, 2H), 3.66 (s, 3H), 2.86 (s, 2H), 1.45-1.35 (m, 2H), 0.93-0.84 (m, 2H).

INTERMEDIATE 10, 10A and 10B

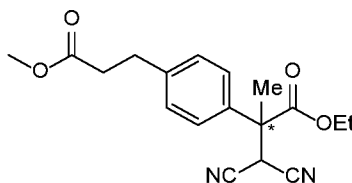
Ethyl-2-(dicyanomethyl)-2-methylbut-3-ynoate and the *S* and *R* isomers thereof



To a flask containing anhydr. LiCl (25.8 mg, 0.609 mmol) in THF (1 mL), was added a solution of ethynylmagnesium bromide (1.3 mL, 0.64 mmol, 0.5M in THF). The reaction was stirred at RT for 0.5 h. The resulting solution was then quickly added dropwise via syringe to a solution of ethyl 3,3-dicyano-2-methylprop-2-enoate (0.609 mL, 0.609 mmol, 1M solution in benzene) (prepared according to Hagiware et. al. Synthesis **1974**, 9, 669) in THF (22.5 mL) at -10°C . The reaction was stirred for 10 min then quenched with sat. aq. NH_4Cl and diluted with water and EtOAc. The layers were separated and the organic layer was dried over anhydr. Na_2SO_4 , and concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using an EtOAc:hexanes gradient to afford the racemic title product **I-10**. The racemic material was resolved using chiral SFC (OJ-H column) to afford isomers **I-10A** (faster eluting) and **I-10B** (slower eluting). ^1H NMR (500 MHz, CDCl_3): δ 4.34 (2H, q, $J = 7.2$ Hz), 4.31 (1H, s), 2.66 (1H, s), 1.80 (3H, s), 1.35 (3H, t, $J = 7.1$ Hz).

INTERMEDIATE 11, 11A and 11B

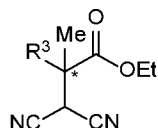
Ethyl 3,3-dicyano-2-(4-(3-methoxy-3-oxopropyl)phenyl)-2-methylpropanoate and the *S* and *R* isomers thereof



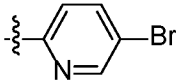
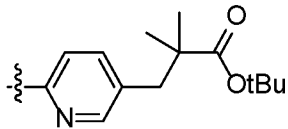
To a flask under an inert atmosphere of nitrogen, containing a solution of methyl 3-(4-iodophenyl)propanoate (1.3 g, 4.48 mmol) in THF (6 mL) at -40°C was slowly added isopropylmagnesium chloride lithium chloride complex (3.9 mL, 5.18 mmol, 1.3 M in THF). The resulting solution was stirred 1 h at -30°C then cooled -50°C . Ethyl 3,3-dicyano-2-methylprop-2-enoate (3.0 mL, 3.05 mmol, 1 M in benzene) (prepared according to Hagiware et. al. Synthesis **1974**, 9, 669) was slowly added and the reaction was stirred for 1 h at -50°C , then quenched with sat. aq. NH_4Cl and diluted with water and EtOAc. The layers were separated and the organic layer was dried over anhydr. Na_2SO_4 , and concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using an EtOAc/petroleum ether (0%-30%) gradient to afford the racemic title product **I-11**. The racemic material was resolved using Chiral SFC (CHIRALPAK[®] AD) to afford isomers **I-11A** (faster eluting) and **I-11B** (slower eluting).

^1H NMR (400 MHz, CDCl_3) δ 7.32 – 7.19 (m, 4H), 4.45 (s, 1H), 4.36 – 4.14 (m, 2H), 3.67 (s, 3H), 2.96 (t, $J = 7.8$ Hz, 2H), 2.64 (dd, $J = 8.4, 7.2$ Hz, 2H), 1.97 (s, 3H), 1.25 (t, $J = 7.1$ Hz, 3H); $m/z = 329$ (M+1).

Using a similar procedure described for the synthesis of intermediate **10** or **11**, the following compounds in **Table 1** were prepared using from commercial starting reagents or compounds known in the literature.

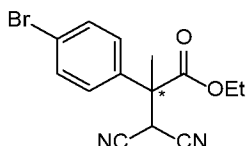
Table 1

Int.	Chiral Resolution Column	R ³	m/z (M+1)
12	-		343
13A 13B	IA		357
14	-		407
15A 15B	AS		329
16	-		371
17	-		357 (M-1)
18	-		^1H NMR (400 MHz, CDCl_3) δ 8.13 – 8.03 (m, 2H), 7.62 – 7.50 (m, 2H), 4.54 (s, 1H), 4.36 – 4.20 (m, 2H), 3.94 (s, 3H), 2.04 (s, 3H), 1.25 (t, $J = 7.1$ Hz, 3H).

19	-		324
20	-		400

INTERMEDIATE 21, 21A and 21B

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



Step A- ethyl 2-(4-bromophenyl)propanoate. To a flask containing ethyl 2-(4-

5 bromophenyl)acetate (20.0 g, 82.9 mmol) in THF (200 mL) at 0 °C was added dropwise a solution of lithium bis(trimethylsilyl) amide (99.6 mL, 99.6 mmol, 1M in THF). The resulting solution was stirred for 1 h at 0 °C then iodomethane (11.7 g, 82.4 mmol) was added dropwise at 0 °C. The reaction mixture was allowed to warm up to RT for 2 h and quenched by the addition of sat. aq. NH₄Cl. The resulting solution was extracted with EtOAc (3X) and the organic layers
10 were combined, dried over anhydr. Na₂SO₄ filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using EtOAc:petroleum ether to afford the title compound.

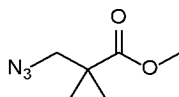
Step B- Ethyl 2-bromo-2-(4-bromophenyl)propanoate. Into a flask were placed ethyl 2-(4-bromophenyl)propanoate (19.5 g, 75.8 mmol), 2,2'-azobisisobutyronitrile (1.25 g, 7.61 mmol)
15 and *N*-bromosuccinimide (16 g, 89.9 mmol) in tetrachloromethane (100 mL). The resulting solution was stirred for 3 h at 80 °C then quenched by the addition of sat. aq. sodium thiosulfate pentahydrate. The resulting solution was extracted with EtOAc (3X) 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 chromatography using EtOAc :
20 petroleum ether to afford the title compound.

Step C- Ethyl 2-(4-bromophenyl)-3,3-dicyano-2-methylpropanoate. Into a flask containing sodium hydride (1.5 g, 62.5 mmol) in DMF (200 mL) at 0 °C was added in portions propanedinitrile (2.4 g, 36.3 mmol). The resulting solution was stirred for 30 min at 0 °C before ethyl 2-bromo-2-(4-bromophenyl) propanoate (10.0 g, 29.8 mmol) was added in portions. The
25 resulting solution was stirred an additional 30 min at 0 °C then 16 h at RT. The reaction was quenched by the addition of brine, extracted with EtOAc (3X). 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 chromatography using EtOAc : petroleum ether to afford the title racemic compound **I-21**. The racemic material was resolved using Chiral SFC (CHIRALPAK[®] OJ-H) to afford isomers **I-21A** (faster eluting) and **I-21B** (slower eluting). ¹H NMR (300 MHz, CDCl₃) δ 7.57 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 2H), 4.44 (s, 1H), 4.33-4.20 (m, 2H), 1.98 (s, 3H), 1.25 (d, *J* = 7.2 Hz, 3H); *m/z* = 319 (M-1).

INTERMEDIATE 22

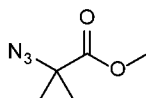
Methyl 1-(azidomethyl)cyclopropane-1-carboxylate



To a closed vial containing a solution of sodium azide (471 mg, 7.25 mmol) in DMSO (40 mL) at RT was added methyl 1-(bromomethyl)cyclopropanecarboxylate (1g, 5.18 mmol). The resulting solution was stirred 48 h at 45 °C. The reaction was allowed to cool down to RT and quenched by the addition of water. The mixture was extracted with Et₂O (2X). The organic layer was dried over anhydr. MgSO₄, filtered and concentrated *in vacuo* to dryness to afford **I-22**. *m/z* = 156 (M+1).

INTERMEDIATE 23

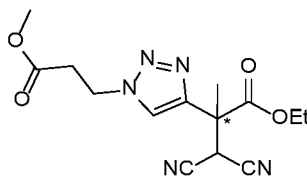
Methyl 2-azido-2-methylpropanoate



To a vial containing a solution of sodium azide (2.6 g, 40 mmol) and methyl 2-bromo-2-methylpropanoate (1.3 mL, 10 mmol) in 10 mL of a 1:1 DCM: water mixture at RT was added tetrabutylammonium hydrogen sulfate (700 mg, 2.0 mmol). The resulting solution was stirred 48 h at RT. The organic layer was washed with water (2X), dried over anhydr. MgSO₄, filtered and concentrated *in vacuo* to dryness to afford **I-23**. ¹H NMR (500 MHz, CDCl₃) δ 3.76 (s, 3H), 1.45 (s, 6H).

INTERMEDIATE 24B

Ethyl 3,3-dicyano-2-(1-(3-methoxy-3-oxopropyl)-1*H*-1,2,3-triazol-4-yl)-2-methylpropanoate



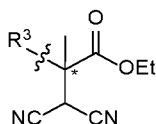
A flask under an inert atmosphere of nitrogen, was charged with ethyl-2-(dicyanomethyl)-2-methylbut-3-ynoate **I-10B** (300 mg, 1.5 mmol), bromotris(triphenylphosphine)copper(I) (144

mg, 0.16 mmol) and DMSO (7.7 mL). To this was added methyl 3-azidopropionate (500 mg, 3.1 mmol) and the reaction was stirred at 50 °C for 18 h. The reaction mixture was diluted with EtOAc, and water. The mixture was extracted with EtOAc (3X). The organic layer was washed with brine (2X), dried over anhydr. MgSO₄, and filtered. The filtrate was concentrated *in vacuo*.

- 5 The residue was purified by silica gel column chromatography with EtOAc:hexane (0-100%) to afford the title compound **I-24B**. ¹H NMR (500 MHz, CDCl₃) δ 7.77 (s, 1H), 4.94 (s, 1H), 4.67 (t, *J* = 6.3 Hz, 2H), 4.30 (qd, *J* = 7.2, 1.3 Hz, 2H), 3.70 (s, 3H), 2.99 (t, *J* = 6.3 Hz, 2H), 1.95 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); *m/z* = 320 (M+1).

Using a similar procedure to that described for the synthesis of intermediate **I-24B**, the following
10 compounds in **Table 2** were prepared from either commercial starting reagents or compounds known in the literature.

Table 2

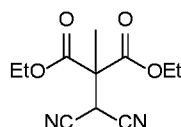


Int.	R ³	<i>m/z</i> (M+1)
25B		306
26B		334
27B		348
28B		346

15

INTERMEDIATE 30

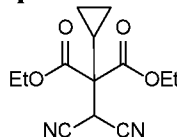
Diethyl 2-(dicyanomethyl)-2-methylmalonate



Using the procedure described in WO2015/088885 intermediate **30** 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).

INTERMEDIATE 31

Diethyl cyclopropyl (dicyanomethyl)propanediote

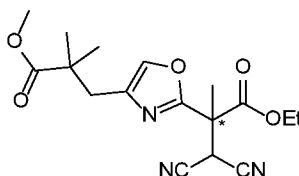


Using the procedure described in WO2015/088885 intermediate **31** was prepared

- 5 ¹H NMR (500 MHz, CDCl₃): δ 4.41 (s, 1 H); 4.38-4.26 (m, 4 H); 1.52-1.45 (m, 1 H); 1.33 (t, *J* = 7.14 Hz, 6 H); 0.86-0.79 (m, 2 H); 0.71-0.66 (m, 2 H).

INTERMEDIATE 32

Ethyl 3,3-dicyano-2-(4-(3-methoxy-2,2-dimethyl-3-oxopropyl)oxazol-2-yl)-2-methylpropanoate



10

- Step A- Ethyl 3-amino-2-methyl-3-oxopropanoate.** To a flask containing ethyl 2-cyanopropanoate (20 g, 157 mmol) at 0 °C was added dropwise chlorotrimethylsilane (40.2 mL, 315 mmol) followed by the dropwise addition of water (5.7 mL, 315 mmol) maintaining the reaction temperature at 0 °C. The reaction mixture was allow to warm up to RT and stirred for 4
- 15 h. The reaction mixture divided into two layers, and the supernatant was discarded. To this was added hexane and the supernatant was discarded again. The residue was then neutralised by the addition of a sat. aq. NaHCO₃ at 0 °C. The mixture was extracted with EtOAc (3X). The organic layer was washed with brine (2X), dried over anhydr. MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to dryness to afford the title compound.

- 20 **Step B- Methyl 3-(2-(1-ethoxy-1-oxopropan-2-yl)oxazol-4-yl)-2,2-dimethylpropanoate.** To a flask containing methyl 5-bromo-2,2-dimethyl-4-oxopentanoate (8.0 g, 33.7 mmol), ethyl 3-amino-2-methyl-3-oxopropanoate (5.0 g, 34.4 mmol) in EtOAc (20 mL) was added silver trifluoromethanesulfonate (8.7 g, 33.7 mmol). The resulting mixture stirred in the dark for 2 h at 90 °C, cooled to RT and filtered. The filtrate was concentrated *in vacuo* and the residue was
- 25 applied onto a C18 column with acetonitrile/water + 0.1% TFA. The residue was purified by silica gel column chromatography with EtOAc:hexane to afford the title compound.

Step C- methyl 3-(2-(2-bromo-1-ethoxy-1-oxopropan-2-yl)oxazol-4-yl)-2,2-

dimethylpropanoate. To a flask containing methyl 3-(2-(1-ethoxy-1-oxopropan-2-yl)oxazol-4-yl)-2,2-dimethylpropanoate (9.0 g, 31.8 mmol) in THF (300 mL) at 0 °C was added dropwise a

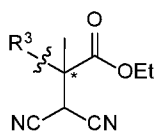
solution of lithium bis(trimethylsilyl)amide (34.9 mL, 34.9 mmol, 1 M in THF). The resulting mixture was stirred for 30 min at 0 °C before *N*-bromosuccinimide (6.2 g, 34.9 mmol) was added in one portion. The resulting mixture was stirred for 30 min at 0 °C then quenched by the addition of sat. aq. NH₄Cl. The mixture was extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. Na₂SO₄, filtered and concentrated *in vacuo*. to dryness. The residue was purified by silica gel chromatography using an EtOAc/hexane gradient to afford the title product.

Step D- Ethyl 3,3-dicyano-2-(4-(3-methoxy-2,2-dimethyl-3-oxopropyl)oxazol-2-yl)-2-methylpropanoate. In a flask containing methyl 3-(2-(2-bromo-1-ethoxy-1-oxopropan-2-

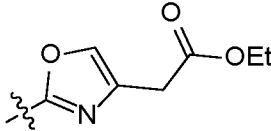
yl)oxazol-4-yl)-2,2-dimethylpropanoate (6.16 g, 17.01 mmol), malononitrile (2.25 g, 34.0 mmol) in THF (200 mL) at 0 °C was added DBU (5.13 mL, 34.0 mmol). The resulting mixture was stirred for 30 min at 0 °C then quenched by the addition of sat. aq. NH₄Cl. The mixture was extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. Na₂SO₄, filtered and concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using an EtOAc/hexane gradient to afford the racemic **I-32**. ¹H NMR (400 MHz, CDCl₃) δ 7.46 (s, 1H), 4.83 (s, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.70 (s, 3H), 2.80 (s, 2H), 2.02 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.23 (d, *J* = 2.8 Hz, 6H); *m/z* = 348 (*M* + 1).

Using a similar procedure to that described for the synthesis of intermediate **32**, the following compounds in **Table 3** were prepared from commercial starting reagents or compounds known in the literature. The racemic material were resolved using chiral SFC (column, see table) to afford isomers **A** (faster eluting) and **B** (slower eluting).

Table 3

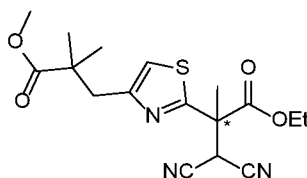


Int.	Chiral Resolution Column	R ³	<i>m/z</i> (M+1)
33A 33B	AD		334

Int.	Chiral Resolution Column	R ³	m/z (M+1)
34A 34B	AD		320

INTERMEDIATE 35, 35A and 35B

Ethyl 3,3-dicyano-2-(4-(3-methoxy-2,2-dimethyl-3-oxopropyl)thiazol-2-yl)-2-methylpropanoate and the *S* and *R* isomers thereof



5

Step A- methyl 3-(2-(1-ethoxy-1-oxopropan-2-yl)thiazol-4-yl)-2,2-dimethylpropanoate. A flask containing ethyl 3-amino-2-methyl-3-thioxopropanoate (6.1 g, 37.8 mmol) and methyl 5-bromo-2,2-dimethyl-4-oxopentanoate (9.44 g, 37.8 mmol) in EtOH (95 mL) was stirred at 50 °C for 1.5h. The reaction was cooled to RT diluted with DCM and triethylamine (5.27 mL, 37.8 mmol) was slowly added the resulting mixture was concentrated *in vacuo* to dryness. The residue was purified by silica gel column chromatography with EtOAc/Hexane gradient to afford the title compound. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.18 (s, 1H); 4.17 (q, *J* = 8.0 Hz, 1H); 4.08 (q, *J* = 8.0 Hz, 2H); 3.05 (s, 3H); 2.88 (s, 2H), 1.45 (d, *J* = 8.0 Hz, 3H), 1.13 (t, *J* = 8.0 Hz, 3H), 1.08 (s, 6H). *m/z* = 300 (M+1).

10

Step B- methyl 3-(2-(2-bromo-1-ethoxy-1-oxopropan-2-yl)thiazol-4-yl)-2,2-dimethylpropanoate. To a flask containing methyl 3-(2-(1-ethoxy-1-oxopropan-2-yl)thiazol-4-yl)-2,2-dimethylpropanoate (10.5 g, 35.1 mmol) in toluene (175 mL) was added HCl (9.64 mL, 38.6 mmol, 4M in dioxane) dropwise, and the resulting mixture was stirred 10 min at RT. The reaction was cooled to 0 °C and KBr (4.59 g, 38.6 mmol) was added followed by the slow addition of H₂O₂ (3.99 mL, 45.6 mmol, 35 wt%). The reaction was stirred at 0 °C for 30 min then quenched by the addition of sodium thiosulfate (22.2 g, 140 mmol), diluted with water and extracted with EtOAc (3X). The organic layers were combined, washed with aq. sat. NaHCO₃, dried over anhydr. MgSO₄, and filtered. The filtrate was concentrated *in vacuo* to dryness to afford the title compound. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.41 (s, 1H); 4.20 (q, *J* = 8.0 Hz,

20

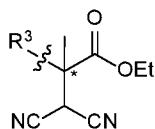
2H); 3.56 (s, 3H); 2.90 (s, 2H), 2.24 (s, 3H), 1.18 (t, $J = 8.0$ Hz, 3H), 1.08 (s, 6H). $m/z = 378$ (M+1).

Step C- ethyl 3,3-dicyano-2-(4-(3-methoxy-2,2-dimethyl-3-oxopropyl)thiazol-2-yl)-2-methylpropanoate. To a flask containing methyl 3-(2-(2-bromo-1-ethoxy-1-oxopropan-2-

5 yl)thiazol-4-yl)-2,2-dimethylpropanoate (520 mg, 1.37 mmol) and malononitrile (182 mg, 2.75 mmol) in THF (14.5 mL) at 0 °C was added dropwise 1,8-Diazabicycloundec-7-ene (0.41 mL, 2.75 mmol). The resulting mixture was stirred for 30 min at 0 °C then quenched by the addition of aq. sat. NH_4Cl and extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. MgSO_4 , and filtered. The filtrate was concentrated *in vacuo*. The
 10 residue was purified by silica gel column chromatography with EtOAc/Hexane gradient to afford the title racemic compound **I-35**. The racemic material was resolved using chiral SFC (CHIRALPAK[®] IC column) to afford isomers **I-35A** (faster eluting) and **I-35B** (slower eluting). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.45 (s, 1H), 5.71 (s, 1H), 4.22 (q, $J = 8.0$ Hz, 2H), 3.58 (s, 3H), 2.94 (m, 2H), 1.86 (s, 3H), 1.17 (t, $J = 8.0$ Hz, 3H), 1.11 (s, 3H) 1.08 (s, 3H); $m/z = 364$
 15 (M+1).

Using a similar procedure to that described for the synthesis of intermediate **35**, the following compound in **Table 4** was prepared. The racemic material were resolved using chiral SFC (column, see table) to afford isomers **A** (faster eluting) and **B** (slower eluting).

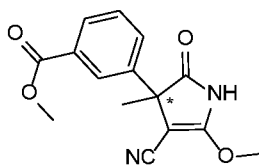
Table 4



Int.	Chiral Resolution Column	R ³	m/z (M+1)
36A 36B	AD-H		348 (M-1)

INTERMEDIATE 37 37A and 37B

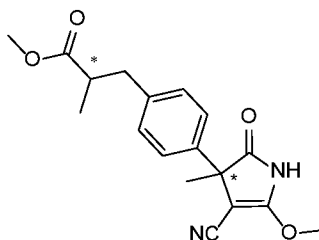
Ethyl 4-cyano-5-ethoxy-3-methyl-2-oxo-2,3-dihydro-1H-pyrrole-3-carboxylate and the *S* and
 25 *R* isomers thereof



To a flask containing a solution of **I-18** (300 mg, 1.0 mmol) in 2.0 mL MeOH at RT was slowly added a solution of NaOMe (0.27 mL, 1.2 mmol, 25 wt.% in MeOH). The resulting solution was stirred 6h at 65 °C. The reaction was allowed to cool down to RT then quenched by the addition of a aq. sol 1M KH₂PO₄ and EtOAc. The mixture was extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. MgSO₄, filtered and concentrated *in vacuo*. to dryness. The residue was purified by silica gel chromatography using an (EtOAc: EtOH 3:1):hexane gradient to afford the racemic title product **I-37**. The racemic material was resolved using Chiral SFC (CHIRALPAK[®] AS-H) to afford isomers **I-37A** (faster eluting) and **I-37B** (slower eluting). ¹H NMR (400 MHz, CDCl₃) δ 8.08 (t, *J* = 1.8 Hz, 1H), 8.00 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.64 (ddd, *J* = 7.9, 2.1, 1.2 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.39 (s, 1H), 4.34 (s, 3H), 3.93 (s, 3H), 1.84 (s, 3H); *m/z* = 287 (M+1).

INTERMEDIATE 38, 38AA, 38AB, 38BA and 38BB

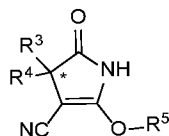
Ethyl 4-cyano-5-ethoxy-3-methyl-2-oxo-2,3-dihydro-1H-pyrrole-3-carboxylate and the *SS*, *SR*, *RS* and *RR* isomers thereof



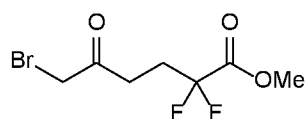
To a flask containing **I-12** (683 mg, 2.0 mmol) in MeOH (4 mL) at RT was added sodium methoxide (0.55 mL, 2.4 mmol, 25 wt.% in MeOH), and the mixture was stirred at 65 °C for 2 h. The reaction was allowed to cool down to RT then quenched by the addition of a 1 M aq. solution of KH₂PO₄ and EtOAc. The mixture was extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. MgSO₄, filtered and concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using an (EtOAc: EtOH 3:1):hexane gradient to afford the racemic title product **I-38**. The racemic material was resolved using chiral SFC (CHIRALPAK[®] AD-H column) to afford isomers **I-38A** (faster eluting) and **I-38B** (slower eluting). Isomer **I-38A** was resolved using chiral SFC (CHIRALPAK[®] AD-H column) to afford isomers **I-38AA** (faster eluting) and **I-38AB** (slower eluting). Isomer **I-38B**

was resolved using chiral SFC (CHIRALPAK[®] AD-H column) to afford isomers **I-38BA** (faster eluting) and **I-38BB** (slower eluting).

Using a similar procedure to that described for the synthesis of intermediate **I-37** or **I-38**, the following compounds in **Table 5** were prepared

Table 5

Int.	Chiral Resolution Column	R ³	R ⁴	R ⁵	m/z (M+1)
39A 39B	AS-H		Me	Et	371
40A 40B	AS-H		Me	Et	239
41A 41B	AS-H			Me	237
42A 42B	IC		Me	Me	334
43A 43B	IC		Me	Me	348 (M-1)

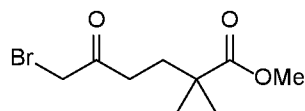
INTERMEDIATE 44**10 Methyl 6-bromo-2,2-difluoro-5-oxohexanoate**

To a flask containing ethyl 2,2-difluoro-5-oxohexanoate (12.0 g, 61.8 mmol) in MeOH (30 mL) at 0 °C was added dropwise bromine (9.9 g, 61.8 mmol). The resulting mixture was stirred for 16 h at RT. The reaction was quenched by the addition of aq. sat. sodium thiosulfate 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 purified by silica

gel column chromatography with EtOAc : petroleum ether to afford the title compound **I-44**. ^1H NMR (300 MHz, CDCl_3) δ 3.88 (s, 2H), 3.23 (s, 3H), 2.99-2.83 (m, 2H), 2.71-2.51 (m, 2H).

INTERMEDIATE 45

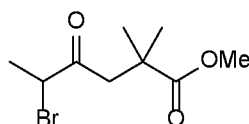
Methyl 6-bromo-2,2-dimethyl-5-oxohexanoate



Intermediate **I-45** was prepared using a similar procedure to that described for the synthesis of intermediate **I-44**, using methyl 2,2-dimethyl-5-oxohexanoate as starting material. ^1H NMR (300 MHz, CDCl_3) δ 3.88 (s, 2H), 3.67 (s, 3H), 2.67-2.61 (m, 2H), 1.81-1.83 (m, 2H), 1.20 (s, 6H).

INTERMEDIATE 46

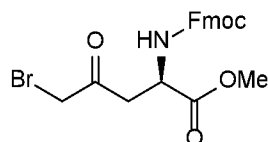
Methyl 5-bromo-2,2-dimethyl-4-oxohexanoate



Intermediate **I-46** was prepared using a similar procedure to that described for the synthesis of intermediate **I-7** using methyl-4-bromo-2,2-dimethylhex-4-enoate as starting material. ^1H NMR (300 MHz, CDCl_3) δ 4.40 (q, $J = 5.1$ Hz, 1H), 3.70 (s, 3H), 3.09 (d, $J = 13.2$ Hz, 2H), 2.94 (d, $J = 13.2$ Hz, 2H), 1.74 (d, $J = 5.1$ Hz, 3H), 1.24 (s, 6H).

INTERMEDIATE 47

(*R*)-methyl -2-{[(9*H*-fluoren-9-yl)methoxy]carbonylamino}-5-bromo-4-oxopentanoate



Step A- (*R*)-methyl- 2-{[(9*H*-fluoren-9-yl)methoxy]carbonylamino}-4-bromopent-4-enoate.

To a flask containing (*R*)-2-({[(9*H*-fluoren-9-yl)methoxy]carbonyl}amino)-4-bromopent-4-enoic acid (1.9 g, 4.56 mmol) in MeOH (30 mL) at 0 °C was added sulfuryl dichloride (62 mg, 0.46 mmol) dropwise. The resulting mixture was stirred at RT for 16 h then quenched by the addition of water. The mixture was extracted with EtOAc (3X). The organic layer was washed with aq. sat. NaHCO_3 and brine, dried over anhydr. Na_2SO_4 , filtered and concentrated *in vacuo* to afford the title product. $m/z = 430, 432$ ($M + 1$).

Step B- (*R*)-methyl- 2-{[(9*H*-fluoren-9-yl)methoxy]carbonylamino}-5-bromo-4-

oxopentanoate. To a flask containing (*R*)-methyl 2-({[(9*H*-fluoren-9-yl)methoxy]carbonyl}amino)-4-bromopent-4-enoate (300 mg, 0.70 mmol) in a DMF (3 mL) -

water (15 mL) mixture at 0 °C was added in portions *N*-bromosuccinimide (136 mg, 0.77 mmol). The resulting mixture was stirred at RT for 16 h then diluted with EtOAc (100 mL), washed with brine, dried over anhydr. Na₂SO₄, filtered and concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using an EtOAc : petroleum ether gradient to afford the title product **I-47** *m/z* = 446, 448 (M + 1).

INTERMEDIATES 48-52

Using a similar procedure described for the synthesis of intermediates **I-10** or **I-11**, the following compounds in **Table 6** were prepared from commercial starting reagents or compounds known in the literature. Racemic material was resolved using chiral SFC or HPLC (column, see table) to afford isomers **A** (faster eluting) and **B** (slower eluting).

Table 6

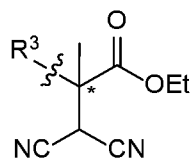
Int.	Chiral Resolution Column	R ³	<i>m/z</i> (M+1)
48A 48B	AD-H		301
49	-		343 (M-1)
50A 50B	OJ-H		271 (M-1)
51A 51B	IF		344
52	-		322

INTERMEDIATES 53-57

Using a similar procedure to that described for the synthesis of intermediate **I-32**, the following compounds in **Table 7** were prepared from commercial starting reagents or compounds known in

the literature. Racemic material was resolved using chiral SFC or HPLC (column, see table) to afford isomers **A** (faster eluting) and **B** (slower eluting).

Table 7



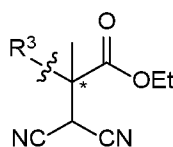
Int.	Chiral Resolution Column	R ³	<i>m/z</i> (M+1)
53A 53B	AS		382
54	-		384
55A 55B	AS-H		362
56A 56B	OJ-H		362
57A 57B	AD-H		557

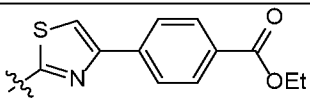
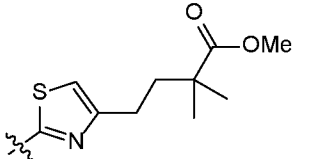
5

INTERMEDIATES 58-59

Using a similar procedure to that described for the synthesis of intermediate **I-35**, the following compounds in **Table 8** was prepared. Racemic material was resolved using chiral SFC or HPLC (column, see table) to afford isomers **A** (faster eluting) and **B** (slower eluting).

10 **Table 8**

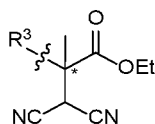


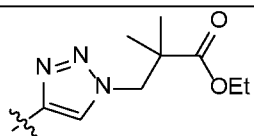
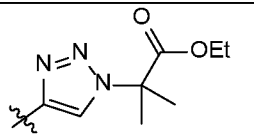
Int.	Chiral Resolution Column	R ³	m/z (M+1)
58A 58B	IF		396 (M-1)
59A 59B	AD-H		376 (M-1)

INTERMEDIATES 60-61

Using a similar procedure to that described for the synthesis of intermediate **I-24**, the following compounds in **Table 9** were prepared from either commercial starting reagents or compounds known in the literature.

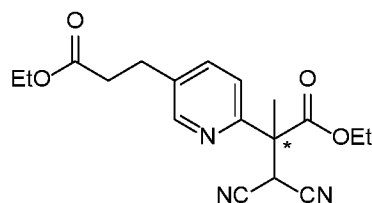
Table 9



Int.	R ³	m/z (M+1)
60		362
61		348

INTERMEDIATE 62

10 Ethyl 3,3-dicyano-2-(5-(3-ethoxy-3-oxopropyl)pyridin-2-yl)-2-methylpropanoate

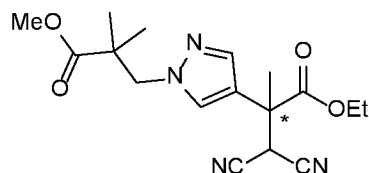


To a flask under an inert atmosphere of nitrogen, containing **I-19** (450 mg, 1.40 mmol) and 2nd generation XPhos precatalyst (chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II), 220 mg, 0.28 mmol) in THF (16 mL) was

added (3-ethoxy-3-oxopropyl)zinc(II) bromide (16.8 mL, 8.38 mmol, 0.5 M in THF). The resulting mixture was stirred for 6 h at 50 °C then quenched by the addition of aq. sat. NH₄Cl and extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. MgSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was then purified by reverse phase HPLC (ACN/water with 0.05% NH₄HCO₃ modifier) to afford the title compound **I-62**. ¹H NMR (300 MHz, CDCl₃) δ 8.41 (d, *J* = 2.4 Hz, 1H), 7.61 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.39 (dd, *J* = 8.1, 0.9 Hz, 1H), 5.20 (s, 1H), 4.25-4.05 (m, 4H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.61 (t, *J* = 7.5 Hz, 2H), 1.95 (s, 3H), 1.23-1.17 (m, 6H); *m/z* = 342 (*M* - 1).

INTERMEDIATE 63, 63A and 63B

- 10 **Ethyl 3,3-dicyano-2-[1-(3-methoxy-2,2-dimethyl-3-oxopropyl)-1*H*-pyrazol-4-yl]-2-methylpropanoate** and the *S* and *R* isomers thereof



- 15 **Step A- Methyl 2,2-dimethyl-3-(1*H*-pyrazol-1-yl)propanoate.** A mixture containing 1*H*-pyrazole (5.2 g, 77 mmol), methyl 2,2-dimethyl-3-(tosyloxy)propanoate (20 g, 69.8 mmol) and cesium carbonate (29.6 g, 91 mmol) in DMF (70 mL) was stirred in a flask at 80 °C for 48 h. The reaction was then quenched by the addition of water and extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. NaSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was then purified by reverse phase HPLC (ACN/water with 0.1% TFA modifier) to afford the title compound *m/z* = 183 (*M* + 1).

- Step B- Methyl 3-[4-(2-ethoxy-2-oxoacetyl)-1*H*-pyrazol-1-yl]-2,2-dimethylpropanoate.** A mixture containing methyl 2,2-dimethyl-3-(1*H*-pyrazol-1-yl)propanoate (3.6 g, 19.76 mmol) and ethyl 2-chloro-2-oxoacetate (10 mL, 89 mmol) was stirred in a flask for 24 h at 100 °C. The reaction mixture was then quenched by the addition of iced water. The pH was adjusted to pH 8 by the addition of NaHCO₃. The resulting mixture was extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. NaSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was then purified by reverse phase HPLC (ACN/water with 0.1% TFA modifier) to afford the title compound *m/z* = 283 (*M* + 1).

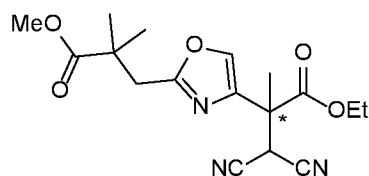
- 30 **Step C- Ethyl 3,3-dicyano-2-[1-(3-methoxy-2,2-dimethyl-3-oxopropyl)-1*H*-pyrazol-4-yl]acrylate.** A flask containing methyl 3-[4-(2-ethoxy-2-oxoacetyl)-1*H*-pyrazol-1-yl]-2,2-

dimethylpropanoate (1.4 g, 4.96 mmol), malononitrile (1.31 g, 19.84 mmol) and piperidine (84 mg, 0.99 mmol) in EtOH (10 mL) was stirred at RT for 16 h. The mixture was concentrated *in vacuo* and the residue was then purified by reverse phase HPLC (ACN/water with 0.1% TFA modifier) to afford the title compound $m/z = 331$ ($M + 1$).

- 5 **Step D- Ethyl 3,3-dicyano-2-[1-(3-methoxy-2,2-dimethyl-3-oxopropyl)-1*H*-pyrazol-4-yl]-2-methylpropanoate.** To a flask under an inert atmosphere of nitrogen, containing ethyl 3,3-dicyano-2-[1-(3-methoxy-2,2-dimethyl-3-oxopropyl)-1*H*-pyrazol-4-yl]acrylate (1.4 g, 4.24 mmol) and lithium chloride (0.36 g, 8.48 mmol) in THF (40 mL) at 0 °C was added methylmagnesium bromide (8.5 mL, 8.5 mmol, 1M in THF) dropwise. The resulting mixture
10 was stirred for 1 h at 0 °C, then the reaction was quenched by the addition of aq. sat. NH_4Cl , extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. NaSO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was then purified by reverse phase HPLC (ACN/water with 0.1% TFA modifier) to afford the title racemic product **I-63**. The racemic material was resolved using chiral SFC (CHIRALPAK[®]
15 AD-H) to afford isomers **I-63A** (faster eluting) and **I-63B** (slower eluting). ^1H NMR (400 MHz, CDCl_3) δ 7.50 (d, $J = 0.8$ Hz, 1H), 7.48 (d, $J = 0.9$ Hz, 1H), 4.41 (s, 1H), 4.34-4.28 (m, 4H), 3.73 (s, 3H), 1.91 (s, 3H), 1.32 (t, $J = 7.2$ Hz, 3H), 1.22 (s, 3H), 1.21 (s, 3H); $m/z = 347$ ($M + 1$).

INTERMEDIATE 64

- 20 **Ethyl 3,3-dicyano-2-[2-(3-methoxy-2,2-dimethyl-3-oxopropyl)oxazol-4-yl]-2-methylpropanoate**



- Step A- Methyl 4-amino-2,2-dimethyl-4-oxobutanoate.** To a flask containing 4-methoxy-3,3-dimethyl-4-oxobutanoic acid (5 g, 31.2 mmol) in DCM (50 mL) at 0 °C was added oxalyl chloride (15 mL, 171 mmol) and a drop of DMF. The resulting mixture was stirred for 3 h at RT.
25 The reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (20 mL), and added to a solution of ammonia hydrate (28%, 20 mL) in THF (20 mL) at 0 °C. The resulting mixture was stirred for 15 min at 0 °C then concentrated *in vacuo*. The residue was dissolved in EtOAc, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo* to afford the title compound.
- 30 **Step B- Methyl 3-[4-(1-ethoxy-1-oxopropan-2-yl)oxazol-2-yl]-2,2-dimethylpropanoate.** A flask containing methyl 4-amino-2,2-dimethyl-4-oxobutanoate (4 g, 25.1 mmol), ethyl 4-bromo-

2-methyl-3-oxobutanoate (6.7 g, 30.2 mmol) and silver trifluoromethanesulfonate (6.78 g, 26.4 mmol) in EtOAc (50 mL) was stirred at 90 °C for 4 h. The reaction mixture was cooled and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by reverse phase HPLC (ACN/water with 0.05% TFA modifier) to afford the title compound.

5 **Step C- Methyl 3-[4-(2-bromo-1-ethoxy-1-oxopropan-2-yl)oxazol-2-yl]-2,2-**

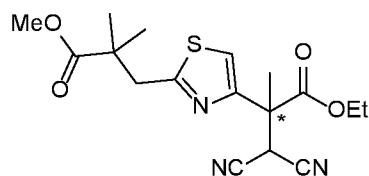
dimethylpropanoate. To a flask, under an inert atmosphere of nitrogen, containing methyl 3-[4-(1-ethoxy-1-oxopropan-2-yl)oxazol-2-yl]-2,2-dimethylpropanoate (1.2 g, 4.24 mmol) in THF (10 mL) at 0 °C was added dropwise lithium bis(trimethylsilyl)amide (5.08 mL, 5.08 mmol). The resulting mixture was stirred for 30 min at 0 °C then a solution of *N*-bromosuccinimide (0.98 g, 5.51 mmol) in THF (5 mL) was added and the mixture was stirred for 30 min at 0 °C. The reaction was quenched by the addition of aq. sat. NH₄Cl, and 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 EtOAc : petroleum ether to afford the title compound.

15 **Step D- Ethyl 3,3-dicyano-2-[2-(3-methoxy-2,2-dimethyl-3-oxopropyl)oxazol-4-yl]-2-**

methylpropanoate. To a flask, under an inert atmosphere of nitrogen, containing methyl 3-[4-(2-bromo-1-ethoxy-1-oxopropan-2-yl)oxazol-2-yl]-2,2-dimethylpropanoate (750 mg, 2.07 mmol) and malononitrile (684 mg, 10.35 mmol) in DMSO (100 mL) at 15 °C was added potassium carbonate (715 mg, 5.18 mmol) in portions. The resulting mixture was stirred for 1 h at RT. The reaction was quenched by the addition of aq. sat. NH₄Cl, 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 EtOAc : petroleum ether to afford the title compound **I-64**. ¹H NMR (300 MHz, CDCl₃) δ 7.60 (s, 1H), 4.79 (s, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.66 (s, 3H), 2.99 (s, 2H), 1.83 (s, 3H), 1.28-1.22 (m, 9H); *m/z* = 348 (*M* + 1).

INTERMEDIATE 65, 65A and 65B

Ethyl 3,3-dicyano-2-[2-(3-methoxy-2,2-dimethyl-3-oxopropyl)thiazol-4-yl]-2-methylpropanoate and the *S* and *R* isomers thereof



30 **Step A- Methyl 4-amino-2,2-dimethyl-4-thioxobutanoate.** To a flask containing methyl 4-amino-2,2-dimethyl-4-oxobutanoate (5.1 g, 32.0 mmol) in THF (200 mL) at 0 °C was added

phosphorus pentasulfide (21.4 g, 96 mmol). The resulting mixture was stirred for 16 h at RT. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc : petroleum ether to afford the title compound.

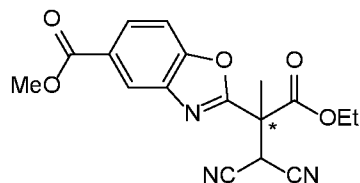
- 5 **Step B- Methyl 3-[4-(1-ethoxy-1-oxopropan-2-yl)thiazol-2-yl]-2,2-dimethylpropanoate.** A flask containing methyl 4-amino-2,2-dimethyl-4-thioxobutanoate (1.65 g, 9.42 mmol) and ethyl 4-bromo-2-methyl-3-oxobutanoate (3.50 g, 9.42 mmol) in EtOH (20 mL) was stirred at 50 °C for 30 min. The reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with MeOH:DCM (0-5%). The residue was diluted with EtOAc and
10 washed with aq. sat. NaHCO₃, dried over anhydr. Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo* to afford the title compound. *m/z* = 300 (*M* + 1).

- Step C- Methyl 3-[4-(2-bromo-1-ethoxy-1-oxopropan-2-yl)thiazol-2-yl]-2,2-dimethylpropanoate.** To a flask under an inert atmosphere of nitrogen, containing methyl 3-[4-(1-ethoxy-1-oxopropan-2-yl)thiazol-2-yl]-2,2-dimethylpropanoate (1.87 g, 6.25 mmol) in THF
15 (40 mL) at 0 °C was added dropwise lithium bis(trimethylsilyl)amide (6.87 mL, 6.87 mmol, 1M in THF). The resulting mixture was stirred at 0 °C for 30 min then a solution of *N*-bromosuccinimide (1.223 g, 6.87 mmol) in THF (4 mL) was added. The resulting mixture was stirred at 0 °C for another 30 min, then quenched by the addition of aq. sat. NH₄Cl, and extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. Na₂SO₄, filtered
20 and the filtrate was concentrated *in vacuo*. The residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA modifier) to afford the title compound. *m/z* = 378, 380 (*M* + 1).

- Step D- Ethyl 3,3-dicyano-2-[2-(3-methoxy-2,2-dimethyl-3-oxopropyl)thiazol-4-yl]-2-methylpropanoate.** To a flask, containing methyl 3-[4-(2-bromo-1-ethoxy-1-oxopropan-2-yl)thiazol-2-yl]-2,2-dimethylpropanoate (560 mg, 1.48 mmol) and malononitrile (489 mg, 7.40
25 mmol) in DMSO (20 mL) at 15 °C was added potassium carbonate (511 mg, 3.70 mmol). The resulting mixture was stirred for 1 h at RT. The reaction was quenched by the addition of aq. sat. NH₄Cl, and 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 reverse phase HPLC (ACN/water with 0.1% TFA modifier) to afford the racemic title
30 compound **I-65**. The racemic material was resolved using Chiral HPLC (CHIRALPAK[®] IF) to afford isomer **I-65A** (faster eluting) and isomer **I-65B** (slower eluting). ¹H NMR (400 MHz, CDCl₃) δ 7.27 (s, 1H), 5.05 (s, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 3.24 (s, 2H), 1.97 (s, 3H), 1.29-1.25 (m, 9H); *m/z* = 364 (*M* + 1).

INTERMEDIATE 66, 66A and 66B

Methyl 2-(1,1-dicyano-3-ethoxy-2-methyl-3-oxopropan-2-yl)benzo[d]oxazole-5-carboxylate
and the *S* and *R* isomers thereof



5 **Step A- 2-(1-Ethoxy-1-oxopropan-2-yl)benzo[d]oxazole-5-carboxylate.** A flask containing methyl 3-amino-4-hydroxybenzoate (5.0 g, 29.9 mmol), and diethyl 2-methylmalonate (15.6 g, 90 mmol) was stirred at 160 °C for 8 h. To this was added 4-methylbenzenesulfonic acid (1.0 g, 5.98 mmol). The resulting mixture was stirred for an additional 10 h at 160 °C then filtered. The filtrate was applied onto silica gel column chromatography with EtOAc : petroleum ether to
10 afford the title compound $m/z = 278$ ($M + 1$).

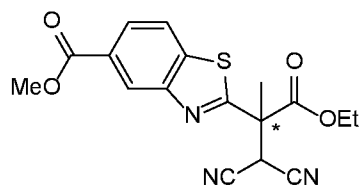
Step B- Methyl 2-(2-bromo-1-ethoxy-1-oxopropan-2-yl)benzo[d]oxazole-5-carboxylate. To a flask, containing methyl 2-(1-ethoxy-1-oxopropan-2-yl)benzo[d]oxazole-5-carboxylate (3 g, 10.82 mmol) in THF (100 mL) at 0 °C was added lithium bis(trimethylsilyl)amide (14.1 mL, 14.10 mmol, 1M in THF). The resulting mixture was stirred for 15 min at 0 °C then a solution of
15 *N*-bromosuccinimide (2.89 g, 16.23 mmol) in THF (10 mL) was added. The resulting mixture was stirred for 30 min at 0 °C then quenched by the addition of aq. sat. NH_4Cl and extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc: petroleum ether to afford the title compound. $m/z = 356$,
20 358 ($M + 1$).

Step C- Methyl 2-(1,1-dicyano-3-ethoxy-2-methyl-3-oxopropan-2-yl)benzo[d]oxazole-5-carboxylate. To a flask containing methyl 2-(2-bromo-1-ethoxy-1-oxopropan-2-yl)benzo[d]oxazole-5-carboxylate (1.5 g, 4.21 mmol) and malononitrile (1.39 g, 21.06 mmol) in DMSO (40 mL) at 15 °C was added potassium carbonate (1.46 g, 10.53 mmol) portionwise. The
25 resulting mixture was stirred for 1 h at RT, then quenched by the addition of aq. sat. NH_4Cl and extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by reverse phase HPLC (ACN/water with 0.05% TFA modifier) to afford racemic **I-66**. The racemic material was resolved using Chiral HPLC (CHIRALPAK® ID) to afford isomer **I-66A** (faster
30 eluting) and isomer **I-66B** (slower eluting) ^1H NMR (400 MHz, CDCl_3) δ 8.51 (s, 1H), 8.20 (d, *J*

= 8.8 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 4.98 (s, 1H), 4.35 (q, J = 7.2 Hz, 2H), 3.99 (s, 3H), 2.17 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H); m/z = 342 ($M + 1$).

INTERMEDIATE 67

Methyl 2-(1,1-dicyano-3-ethoxy-2-methyl-3-oxopropan-2-yl)benzo[d]thiazole-5-carboxylate



Step A- Methyl 2-(1-ethoxy-1-oxopropan-2-yl)benzo[d]thiazole-5-carboxylate. A flask under an inert atmosphere of nitrogen, containing methyl 3-amino-4-mercaptobenzoate hydrochloride (8.4 g, 38.20 mmol) and ethyl 2-cyanopropanoate (4.9 g, 38.20 mmol) was stirred for 2 h at 120 °C. The reaction was quenched by the addition of water and extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc : petroleum ether (0-50%). The residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA modifier) to afford the title compound. m/z = 294 ($M + 1$).

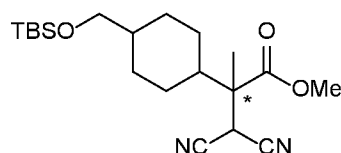
Step B- Methyl 2-(2-bromo-1-ethoxy-1-oxopropan-2-yl)benzo[d]thiazole-5-carboxylate. To a flask under an inert atmosphere of nitrogen, containing methyl 2-(1-ethoxy-1-oxopropan-2-yl)benzo[d]thiazole-5-carboxylate (457 mg, 1.56 mmol) in THF (20 mL) at 0 °C was added dropwise a solution of lithium bis(trimethylsilyl) amide (1.56 mmol, 1.56 mL, 1 M in THF). The mixture was stirred for 15 min at 0 °C before *N*-bromosuccinimide (305 mg, 1.714 mmol) was added. The resulting mixture was stirred for 30 min at 0 °C, then quenched by the addition of aq. sat. NH_4Cl and extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc: petroleum ether (0-10%) to afford the title compound. m/z = 372, 374 ($M + 1$).

Step C. Methyl 2-(1,1-dicyano-3-ethoxy-2-methyl-3-oxopropan-2-yl)benzo[d]thiazole-5-carboxylate. To a flask containing methyl 2-(2-bromo-1-ethoxy-1-oxopropan-2-yl)benzo[d]thiazole-5-carboxylate (269 mg, 0.72 mmol) and malononitrile (286 mg, 4.34 mmol) in DMSO (5 mL) at 15 °C was added potassium carbonate (300 mg, 2.17 mmol). The resulting mixture was stirred for 1 h at RT, then the reaction mixture was quenched by the addition of aq. sat. NH_4Cl and extracted with EtOAc (3X). The organic layers were combined, washed with

brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA modifier) to afford the title compound. ^1H NMR (400 MHz, CDCl_3) δ 8.76 (d, $J = 1.6$ Hz 1H), 8.17 (dd, $J = 1.6, 8.4$ Hz, 1H), 8.09 (d, $J = 8.4$ Hz, 1H), 5.27 (s, 1H), 4.38 (q, $J = 7.2$ Hz, 2H), 3.99 (s, 3H), 2.17 (s, 3H), 1.34 (t, $J = 7.2$ Hz, 3H); $m/z = 358$ ($M + 1$).

INTERMEDIATE 68

Methyl 2-(4-(((tert-butyl)dimethylsilyl)oxy)methyl)cyclohexyl)-3,3-dicyano-2-methylpropanoate



Step A- (4-Bromocyclohexyl)methanol. To a flask containing LiAlH_4 (5.6 g, 148 mmol) in THF (200 mL) at 0°C was added dropwise a solution of ethyl 4-bromocyclohexane carboxylate (31.2 g, 133 mmol) in THF (50 mL). The resulting mixture was stirred at 0°C for 1 h. The reaction mixture was slowly quenched by the addition of water (5.6 mL) at 0°C . Then to this, was added sodium hydroxide (15%, 5.6 mL) and water (16.8 mL). The resulting mixture was stirred for 15 min. To this was added anhydr. MgSO_4 . The resulting mixture was stirred for 15 min, and filtered. The filtrate was concentrated *in vacuo* to give the title compound.

Step B- [(4-Bromocyclohexyl)methoxy](tert-butyl)dimethylsilane. To a flask containing (4-bromocyclohexyl)methanol (25.1 g, 130 mmol) and *tert*-butylchlorodimethylsilane (21.6 g, 143 mmol) in DMF (100 mL) at 0°C was added portionwise imidazole (11.5 g, 169 mmol). The resulting mixture was stirred for 3 h at RT. The reaction was then quenched by the addition of water and extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. NaSO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography using an EtOAc : petroleum ether gradient to afford the title compound.

Step C- Methyl 2-(4-(((tert-butyl)dimethylsilyl)oxy)methyl)cyclohexyl)-2-oxoacetate. To a flask under an inert atmosphere of nitrogen, containing magnesium turnings (0.79 g, 32.5 mmol), a few drops of [(4-bromocyclohexyl)methoxy](tert-butyl)dimethylsilane and iodine (0.21 g, 0.81 mmol) in diethyl ether (5 mL) was heated to reflux. A solution of [(4-bromocyclohexyl)methoxy](tert-butyl)dimethylsilane (5 g, 16.27 mmol) in diethyl ether (40 mL) was added dropwise to the reaction over approximately 1.5 h, maintaining the reaction mixture at

reflux. The reaction was stirred at reflux for an additional 1 h then cooled to RT. This reaction mixture was added dropwise to a flask under an inert atmosphere of nitrogen, containing dimethyl oxalate (2.50 g, 21.15 mmol) in a diethyl ether (30 mL) - THF (50 mL) mixture at 0 °C. The resulting mixture was stirred for 2 h at RT. The reaction was then quenched by the addition of aq. sat. NH₄Cl and extracted with diethyl ether (3X). The organic layers were combined, washed with brine, dried over anhydr. NaSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography using an EtOAc : petroleum ether gradient to afford the title compound ¹H NMR (400 MHz, CDCl₃) δ 3.92-3.88 (m, 3H), 3.48-3.41 (m, 2H), 2.10-1.80 (m, 4H), 1.70-1.25 (m, 4H), 1.10-0.95 (m, 1H), 0.95-0.90 (m, 10H), 0.07-0.05 (m, 6H).

Step D- Methyl 2-(4-{{(tert-butyldimethylsilyl)oxy}methyl}cyclohexyl)-3,3-dicyanoacrylate.

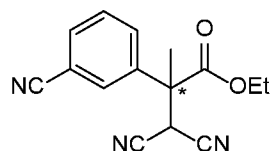
Into a flask were placed methyl 2-(4-{{(tert-butyldimethylsilyl)oxy}methyl}cyclohexyl)-2-oxoacetate (2.7 g, 8.59 mmol), malononitrile (1.13 g, 17.17 mmol), 3-aminopropanoic acid (0.23 g, 2.58 mmol), and water (20 mL). The resulting mixture was stirred for 15 min at RT before ethanol (20 mL) was added, and the mixture was stirred at RT for an additional 2 h. The reaction was then quenched by the addition of brine and extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. NaSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography using an EtOAc : petroleum ether gradient to afford the title compound.

Step E- Methyl 2-(4-{{(tert-butyldimethylsilyl)oxy}methyl}cyclohexyl)-3,3-dicyano-2-methylpropanoate.

To a flask, under an inert atmosphere of nitrogen, containing methyl 2-(4-{{(tert-butyldimethylsilyl)oxy}methyl}cyclohexyl)-3,3-dicyanoacrylate (2.2 g, 6.07 mmol) and lithium chloride (0.77 g, 18.20 mmol) in THF (30 mL) at 0 °C was added methylmagnesium bromide (4.1 mL, 12.14 mmol, 3M in diethyl ether) dropwise. The resulting mixture was stirred for 1 h at 0 °C, then quenched by the addition of aq. sat. NH₄Cl and extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. NaSO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography using an EtOAc : petroleum ether gradient to afford the title compound **I-68**. ¹H NMR (400 MHz, CDCl₃) δ 4.34-4.30 (m, 1H), 3.83-3.82 (brs, 3H), 3.41 (d, *J* = 6.4 Hz, 2H), 1.90-1.65 (m, 5H), 1.57 (s, 3H), 1.40-1.35 (m, 1H), 1.15-0.80 (m, 13H), 0.06-0.04 (m, 6H); *m/z* = 377 (*M* - 1).

INTERMEDIATE 69, 69A and 69B

Ethyl 3,3-dicyano-2-(3-cyanophenyl)-2-methylpropanoate and the *S* and *R* isomers thereof



Step A- Ethyl 2-bromo-2-(3-bromophenyl)propanoate. A flask, under an inert atmosphere of nitrogen, containing ethyl 2-(3-bromophenyl)propanoate (21 g, 73.5 mmol), *N*-bromosuccinimide (15.7 g, 88 mmol) and azodiisobutyronitrile (1.2 g, 7.35 mmol) in tetrachloromethane (300 mL) was stirred at 80 °C for 1.5 h. The reaction mixture was cooled to RT, quenched by the addition of aq. sat. sodium bisulfate, 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 purified by silica gel column chromatography with EtOAc : petroleum ether (0-30%) to afford the title compound.

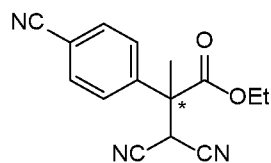
Step B- Ethyl 2-(3-bromophenyl)-3,3-dicyano-2-methylpropanoate. To a flask, under an inert atmosphere of nitrogen, containing malononitrile (1.24 g, 18.8 mmol) in DMF (30 mL) at 0 °C was added in portions sodium hydride (0.56 g, 14.1 mmol, 60%). The mixture was stirred for 30 min at 0 °C before ethyl 2-bromo-2-(3-bromophenyl)propanoate (3.5 g, 9.37 mmol) was added. The resulting mixture was stirred for 1 h at 0 °C, then quenched by the addition of water 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 purified by silica gel column chromatography with EtOAc : petroleum ether (0-50%) to afford the title compound. ¹H NMR (300 MHz, CDCl₃) δ 7.59-7.51 (m, 2H), 7.36-7.29 (m, 2H), 4.47 (s, 1H), 4.34-4.23 (m, 2H), 1.98 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H).

Step C- Ethyl 3,3-dicyano-2-(3-cyanophenyl)-2-methylpropanoate A flask under an inert atmosphere of nitrogen, containing ethyl 2-(3-bromophenyl)-3,3-dicyano-2-methylpropanoate (2.5 g, 7.39 mmol), 1,1'-bis(diphenylphosphino)ferrocene (0.82 g, 1.479 mmol), zinc cyanide (1.13 g, 9.61 mmol), zinc (0.24 g, 3.70 mmol), tris(dibenzylideneacetone)dipalladium chloroform adduct (0.76 g, 0.739 mmol) in DMA (25 mL) was stirred for 16 h at 120 °C. The mixture was cooled to RT, quenched by the addition of water 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 purified by silica gel column chromatography with EtOAc : petroleum ether (0-50%) to afford the racemic title compound **I-69**. The racemic material was resolved using Chiral HPLC (Chiralcel OJ-H) to afford isomer **I-69A** (faster eluting) and isomer **I-69B** (slower eluting) ¹H NMR (300 MHz, CDCl₃) δ 7.76-7.57

(m, 4H), 4.49 (s, 1H), 4.39-4.23 (m, 2H), 2.02 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H); $m/z = 266$ ($M - 1$).

INTERMEDIATE 70A

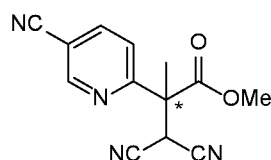
Ethyl 3,3-dicyano-2-(4-cyanophenyl)-2-methylpropanoate



A flask under an inert atmosphere of nitrogen, containing **I-21A** (320 mg, 1.00 mmol), 1,1'-bis(diphenylphosphino)ferrocene (50 mg, 0.09 mmol), zinc powder (32 mg, 0.49 mmol), zinc cyanide (150 mg, 1.29 mmol) and tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (60 mg, 0.06 mmol) in DMA (10 mL) was stirred for 2 h at 120 °C. The reaction was cooled to RT and quenched by the addition of water and extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc : petroleum ether (0-20%) to afford the title compound **I-70A**. ^1H NMR (400 MHz, CDCl_3) δ 7.79 (d, $J = 8.0$ Hz, 2H), 7.55 (d, $J = 8.4$ Hz, 2H), 4.50 (s, 1H), 4.39-4.26 (m, 2H), 2.04 (s, 3H), 1.29 (t, $J = 7.2$ Hz, 3H); $m/z = 266$ ($M - 1$).

INTERMEDIATE 71, 71A and 71B

Methyl 3,3-dicyano-2-(5-cyanopyridin-2-yl)-2-methylpropanoate and the *S* and *R* isomers thereof



Step A- Ethyl 2 (5-bromopyridin-2-yl)propanoate. To a flask, containing ethyl 2-(5-bromopyridin-2-yl)acetate (4 g, 16.39 mmol) in THF (20 mL) at 0 °C was added dropwise lithium bis(trimethylsilyl)amide (18.2 mL, 18.7 mmol, 1 M in THF). The resulting solution was stirred at 0 °C for 30 min, and iodomethane (2.3 g, 16.20 mmol) was added. The resulting solution was stirred 2 h at RT then quenched by the addition of water and extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc : petroleum ether (0-10%) to afford the title compound.

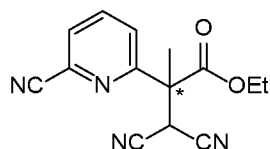
Step B- Ethyl 2-(5-cyanopyridin-2-yl)propanoate. A flask, under an inert atmosphere of nitrogen, containing ethyl 2-(5-bromopyridin-2-yl)propanoate (3.8 g, 14.72 mmol), dicyanozinc (2.25 g, 19.14 mmol), zinc (0.48 g, 7.36 mmol), tris(dienzylideneacetone) dipalladium-chloroform adduct (1.52 g, 1.472 mmol) and 1,1'-ferrocenebis (diphenylphosphine) (1.63 g, 2.94 mmol) in DMA (30 mL) was stirred at 120 °C for 2 h. The mixture was cooled, diluted with a mixture DCM /MeOH (1/1) (100 mL). The solid was filtered out, and the filtrate was concentrated *in vacuo*. Water was added to the residue and the mixture was 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 purified by silica gel column chromatography with MeOH:DCM (0-10%) to afford the title compound.

Step C- Ethyl 2-bromo-2-(5-cyanopyridin-2-yl)propanoate. A flask, under an inert atmosphere of nitrogen, containing ethyl 2-(5-cyanopyridin-2-yl)propanoate (2.5 g, 12.24 mmol), *N*-bromosuccinimide (2.83 g, 15.91 mmol) and 2,2'-azobisisobutyronitrile (0.20 g, 1.22 mmol) in carbontetrachloride (25 mL) was stirred for 4 h at 80 °C. The reaction was cooled, quenched by the addition of water and extracted with DCM (3X). The organic layers were combined, 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 EtOAc : petroleum ether (0-10%) to afford the title compound.

Step D- Ethyl 3,3-dicyano-2-(5-cyanopyridin-2-yl)-2-methylpropanoate. To a flask containing sodium hydride (0.28 g, 7.06 mmol) in DMF (12 mL) at 0 °C, was added dropwise a solution of malononitrile (0.47 g, 7.06 mmol) in DMF (2 mL). The mixture was stirred for 15 min at 0 °C, then ethyl 2-bromo-2-(5-cyanopyridin-2-yl)propanoate (1.0 g, 3.53 mmol) was added. The reaction mixture was stirred for 2 h at 0 °C. The reaction was quenched by the addition of water 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 purified by silica gel column chromatography with EtOAc : petroleum ether (0-10%) to afford the racemic title compound **I-71**. The racemic material was resolved using Chiral HPLC (CHIRALPAK[®] AS-H) to afford isomer **I-71A** (faster eluting) and isomer **I-71B** (slower eluting). ¹H NMR (300 MHz, CDCl₃) δ 8.85 (dd, *J* = 2.1, 0.9 Hz, 1H), 8.07 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.65 (dd, *J* = 8.4, 0.9 Hz, 1H), 5.11 (s, 1H), 4.29-4.18 (m, 2H), 2.00 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H); *m/z* = 269 (*M* + 1).

INTERMEDIATE 72

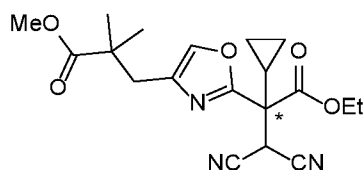
Ethyl 3,3-dicyano-2-(6-cyanopyridin-2-yl)-2-methylpropanoate



A flask purged and maintained with an inert atmosphere of nitrogen, containing **I-52** (197 mg, 1.68 mmol), tris(dibenzylideneacetone)dipalladium chloroform adduct (145 mg, 0.14 mmol), 1,1'-bis(diphenylphosphino)ferrocene (155 mg, 0.28 mmol) and zinc (45.7 mg, 0.698 mmol), in DMA (15 mL) was stirred for 90 min at 120 °C. The reaction was cooled to RT, quenched by the addition of water 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 purified by silica gel column chromatography with EtOAc : petroleum ether to afford the title compound **I-72**. ¹H NMR (400 MHz, CDCl₃) δ 8.02 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.80-7.76 (m, 2H), 5.17 (s, 1H), 4.35-4.25 (m, 2H), 2.06 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); *m/z* = 269 (*M* + 1).

INTERMEDIATE 73

Ethyl 3,3-dicyano-2-cyclopropyl-2-[4-(3-methoxy-2,2-dimethyl-3-oxopropyl)oxazol-2-yl]propanoate



Step A- Ethyl 3-amino-2-cyclopropyl-3-oxopropanoate. In a flask containing ethyl 2-cyano-2-cyclopropylacetate (20 g, 131 mmol) and chlorotrimethylsilane (28.4 g, 261 mmol) was added water (4.7 mL, 261 mmol) dropwise at 0 °C. The resulting mixture was stirred for 5 h at RT. The reaction mixture was divided into two layers, and the supernatant was discarded. To this was added hexane (100 mL), and the supernatant was discarded again. The aqueous layer was neutralised by the addition of aq. sat. NHCO₃ at 0 °C. 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 washed with hexane, and dried to afford the title compound.

Step B- Methyl 3-(2-(1-cyclopropyl-2-ethoxy-2-oxoethyl)oxazol-4-yl)-2,2-dimethylpropanoate. A flask containing ethyl 3-amino-2-cyclopropyl-3-oxopropanoate (4.7 g, 27.4 mmol), methyl 5-bromo-2, 2-dimethyl-4-oxopentanoate (5.0 g, 21.09 mmol) and silver (I) trifluoromethanesulfonate (5.96 g, 23.20 mmol) in EtOAc (10 mL) was stirred for 16 h at 80 °C. The resulting mixture was filtered, and the solid was washed with EtOAc. The filtrate was

concentrated *in vacuo*. The residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA modifier) to afford the title compound.

Step C- Methyl 3-[2-(1-bromo-1-cyclopropyl-2-ethoxy-2-oxoethyl)oxazol-4-yl]-2,2-

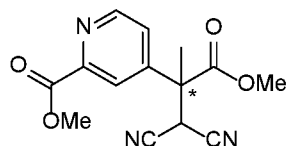
dimethylpropanoate. To a flask under an inert atmosphere of nitrogen, containing methyl 3-[2-(1-cyclopropyl-2-ethoxy-2-oxoethyl)oxazol-4-yl]-2,2-dimethylpropanoate (3.4 g, 10.99 mmol) in THF (60 mL) at 0 °C was added dropwise lithium bis(trimethylsilyl)amide (13.19 mL, 13.19 mmol, 1M in THF). The resulting mixture was stirred 30 min at 0 °C before a solution of 1-bromopyrrolidine-2, 5-dione (2.93 g, 16.49 mmol) in THF (30 mL) was added at 0 °C. The resulting mixture was stirred for 30 min at 0 °C then quenched by the addition of aq. sat. NH₄Cl 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 purified by silica gel column chromatography with EtOAc : petroleum ether (0-10%) to afford the title compound

Step D- Ethyl 3,3-dicyano-2-cyclopropyl-2-[4-(3-methoxy-2,2-dimethyl-3-oxopropyl)oxazol-2-yl]propanoate.

To a flask containing methyl 3-[2-(1-bromo-1-cyclopropyl-2-ethoxy-2-oxoethyl)oxazol-4-yl]-2,2-dimethylpropanoate (840 mg, 2.16 mmol) and malononitrile (858 mg, 12.98 mmol) in DMSO (5 mL) at 15 °C was added potassium carbonate (897 mg, 6.49 mmol) in portions. The resulting mixture was stirred for 1.5 h at 15 °C then quenched by the addition of aq. sat. NH₄Cl, extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by reverse phase HPLC (ACN/water with 0.05% TFA modifier) to afford the title compound **I-73**. ¹H NMR (300 MHz, CDCl₃) δ 7.44 (s, 1H), 4.67 (s, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.68 (s, 3H), 2.79 (s, 2H), 1.67-1.58 (m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.22 (s, 3H), 1.21 (s, 3H), 0.85-0.77 (m, 2H), 0.66- 0.57 (m, 2H).; *m/z* = 374 (*M* + 1).

INTERMEDIATE 74, 74A and 74B

Methyl 4-(1,1-dicyano-3-methoxy-2-methyl-3-oxopropan-2-yl)picolinate and the *S* and *R* isomers thereof



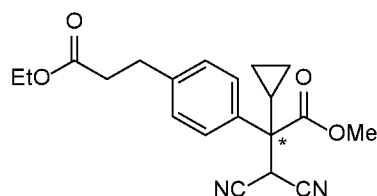
Step A- Methyl 4-(2-methoxy-2-oxoethyl)picolinate. To a flask, under an inert atmosphere of nitrogen, containing methyl 2-(2-bromopyridin-4-yl)acetate (2.0g, 8.69 mmol), palladium(II) acetate (0.46 g, 2.09 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (2.31 g, 4.17 mmol) in

DMF (44 ml) was added *N,N*-diisopropylethylamine (7.59 ml, 43.5 mmol) in MeOH (31.7 ml, 782 mmol). The flask was flushed with CO and stirred 4h under 1 atm of CO (balloon). The reaction was quenched by the addition of EtOAc and filtered. The organic layers were combined, washed with water and brine, dried over anhydr. Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc : hexane (0-100%) to afford the title compound.

Step B- Methyl 4-(1-methoxy-1-oxopropan-2-yl)picolinate. To a flask, under an inert atmosphere of nitrogen, containing lithium bis(trimethylsilyl)amide (5.26 mL, 5.26 mmol, 1M in THF) at 0 °C was slowly added a solution of methyl 4-(2-methoxy-2-oxoethyl)picolinate (1.1g, 5.26 mmol) in THF (10 mL), followed by methyl iodide (0.329 ml, 5.26 mmol). The resulting mixture was stirred at 0 °C for 45 min then concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc: hexane (0-100%) to afford the title compound.

Step C- Methyl 4-(2-bromo-1-methoxy-1-oxopropan-2-yl)picolinate. To a flask containing methyl 4-(1-methoxy-1-oxopropan-2-yl)picolinate (600 mg, 2.15 mmol) in MeCN (13 mL) was added magnesium perchlorate (316 mg, 1.42 mmol). The mixture was stirred 5 min at RT before *N*-bromosuccinimide (928 mg, 5.16 mmol) was added. The mixture was stirred at RT for 2 days, then concentrated *in vacuo*. The residue was diluted in EtOAc. The organic layers were combined, washed with water, dried over anhydr. Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc:hexane to afford the title compound.

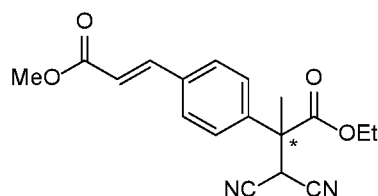
Step D- Methyl 4-(1,1-dicyano-3-methoxy-2-methyl-3-oxopropan-2-yl)picolinate. To a flask, under an inert atmosphere of nitrogen, containing sodium hydride (53.7 mg, 1.34 mmol, 60%w) in DMF (5 mL) at 0 °C was added dropwise a solution of malononitrile (89 mg, 1.343 mmol) in DMF (5 mL), followed by a solution of methyl 4-(2-bromo-1-methoxy-1-oxopropan-2-yl)picolinate (390 mg, 1.03 mmol) in DMF (5 mL). The reaction was allowed to warm up to RT and stirred for 1 h at RT. The reaction was quenched by the addition of aq. sat. NH₄Cl and extracted with EtOAc (3X). The organic layers were combined, 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:hexane (0-100%) to afford the title racemic compound **I-74**. The racemic material was resolved using Chiral SFC (CHIRALPAK® IC) to afford isomer **I-74A** (faster eluting) and isomer **I-74B** (slower eluting). ¹H-NMR (400 MHz, CDCl₃): δ 2.033(s, 3H), 3.820(s, 3H), 4.015(s, 3H), 4.539(s, 1H), 7.454-7.478(d, 1H), 8.103-8.108(s, 1H), 8.820-8.839(d, 1H), *m/z* = 288 (M+1).

INTERMEDIATE 75A**Methyl 3,3-dicyano-2-cyclopropyl-2-[4-(3-ethoxy-3-oxopropyl)phenyl]propanoate****Step A- Methyl 2-(4-bromophenyl)-3,3-dicyano-2-cyclopropylpropanoate**

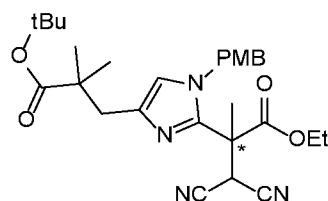
- 5 To a flask, under an inert atmosphere of nitrogen containing 1,4-dibromobenzene (4.82 g, 20.43 mmol) in THF (60 mL) at -70 °C was added dropwise *sec*-butyllithium (17.0 mL, 22.14 mmol). The mixture was stirred for 30 min at -70 °C before a solution of methyl 3,3-dicyano-2-cyclopropylacrylate (3 g, 17.03 mmol) in THF (20 mL) was added dropwise at -70 °C. The resulting mixture was stirred for 30 min at RT, then quenched by the addition of aq. sat. NH₄Cl
- 10 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 purified by silica gel column chromatography with EtOAc : petroleum ether (0-40%) to afford the title racemic compound. The racemic material was resolved using Chiral HPLC (CHIRALPAK[®] AD-H) to afford isomer **A** (faster eluting) and isomer **B** (slower eluting). ¹H
- 15 NMR (400 MHz, CDCl₃) δ 7.58 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 4.45 (s, 1H), 3.77 (s, 3H), 1.69-1.62 (m, 1H), 1.05-0.98 (m, 1H), 0.92-0.79 (m, 2H), 0.53-0.47 (m, 1H); *m/z* = 331, 333 (*M* - 1).

Step B methyl 3,3-dicyano-2-cyclopropyl-2-[4-(3-ethoxy-3-oxopropyl)phenyl] propanoate.

- 20 To a flask, under an inert atmosphere of nitrogen, containing methyl 2-(4-bromophenyl)-3,3-dicyano-2-cyclopropylpropanoate isomer **A** (300 mg, 0.900 mmol) and second generation Xphos precatalyst (chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II), 142 mg, 0.180 mmol) in THF (10 mL) was added (3-ethoxy-3-oxopropyl)zinc(II) bromide (10.8 mL, 5.40 mmol). The resulting mixture was stirred at 50 °C for 6 h. The reaction was quenched by the addition of aq. sat. NH₄Cl and extracted with EtOAc
- 25 (3X). The organic layers were combined, 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 EtOAc : petroleum ether (0-40%) to afford the title compound **I-75A**. ¹H
- 30 NMR (300 MHz, CDCl₃) δ 7.34 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 4.42 (s, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 2.95 (t, *J* = 7.8 Hz, 2H), 2.61 (t, *J* = 7.8 Hz, 2H), 1.67-1.59 (m, 1H), 1.20 (t, *J* = 7.2 Hz, 3H), 1.02-0.78 (m, 3H), 0.50-0.41 (m, 1H); *m/z* = 353 (*M* - 1).

INTERMEDIATE 76A**Methyl (*E*)-3-(4-(1,1-dicyano-3-ethoxy-2-methyl-3-oxopropan-2-yl)phenyl)acrylate**

A flask, under an inert atmosphere of nitrogen, containing ethyl 2-(4-chlorophenyl)-3,3-dicyano-2-methylpropanoate (Intermediate 2A in WO 2016/081668) (500 mg, 1.80 mmol) methyl acrylate (325 μ l, 3.61 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (52.4 mg, 0.181 mmol), tris(dibenzylideneacetone)dipalladium(0) (42.2 mg, 0.045 mmol) and dicyclohexylmethylamine (464 μ l, 2.168 mmol) in dioxane (9 mL) was stirred 2 h at 100 °C. The reaction was cooled, quenched by the addition of water 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 purified by silica gel column chromatography with EtOAc : petroleum ether (0-10%) to afford the title compound **I-76A**. ¹H NMR (400 MHz, CDCl₃) δ 7.67 (d, *J* = 16.0 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.44 – 7.37 (m, 2H), 6.47 (d, *J* = 16.0 Hz, 1H), 4.48 (s, 1H), 4.35 – 4.18 (m, 2H), 3.82 (s, 3H), 2.00 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). *m/z* = 327 (M+1).

INTERMEDIATE 77**Ethyl 2-{4-[3-(*tert*-butoxy)-3-oxopropyl]-1-(4-methoxybenzyl)-1*H*-imidazol-2-yl}-3,3-dicyano-2-methylpropanoate**

Step A- *tert*-Butyl 3-(1*H*-imidazol-4-yl)acrylate. To a flask containing 1*H*-imidazole-4-carbaldehyde (10 g, 104 mmol) and *tert*-butyl 2-(diethoxyphosphoryl)acetate (39.4 g, 156 mmol) in DMF (100 mL) at 0 °C was added in portions sodium hydride (4.99 g, 208 mmol, 60%w). The resulting mixture was stirred for 3 h at 95 °C then cooled to RT and quenched by the addition of aq. sat. NaHCO₃ and extracted with EtOAc (3X). The organic layers were combined, washed with water and brine, dried over anhydr. Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc: petroleum ether (0-80%) to afford the title compound.

Step B- *tert*-Butyl 3-(1-(4-methoxybenzyl)-1*H*-imidazol-4-yl)acrylate. To a flask containing *tert*-butyl 3-(1*H*-imidazol-4-yl)acrylate (9.3 g, 43.1 mmol) and potassium carbonate (11.9 g, 86 mmol) in DMF (100 mL) at 0 °C was added dropwise 1-(chloromethyl) -4-methoxybenzene (10.1 g, 64.6 mmol). The resulting mixture was stirred for 2 h at RT then quenched by the
5 addition of water and extracted with EtOAc (3X). The organic layers were combined, washed with water and brine, dried over anhydr. Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc : petroleum ether (10-60%) to afford the title compound.

Step C- *tert*-Butyl 3-[1-(4-methoxybenzyl)-1*H*-imidazol-4-yl]propanoate. To a flask
10 containing *tert*-butyl 3-(1-(4-methoxybenzyl)-1*H*-imidazol-4-yl)acrylate (10 g, 31.8 mmol) in MeOH (100 mL) was added palladium on carbon (wet, 1.5 g, 10%) at RT. The flask was evacuated and flushed three times with nitrogen, followed by flushing with hydrogen. The mixture was stirred 4 h at RT under an atmosphere of hydrogen (1.5 atm). The mixture was filtered and the residue rinsed with MeOH. The filtrate was concentrated *in vacuo* to afford the
15 title compound.

Step D- *tert*-Butyl 3-[2-(2-ethoxy-2-oxoacetyl)-1-(4-methoxybenzyl)-1*H*-imidazol-4-yl]propanoate. To a flask containing *tert*-butyl 3-[1-(4-methoxybenzyl)-1*H*-imidazol-4-yl]propanoate (8.5 g, 26.9 mmol) in DCM (100 mL) at -40 °C was added dropwise ethyl 2-chloro-2-oxoacetate (11.0 g, 81 mmol) followed by the dropwise addition of *N*-ethyl-*N*-
20 isopropylpropan-2-amine (10.4 g, 81 mmol) at -40 °C. The mixture was stirred for 6 h at RT then quenched by the addition of aq. sat. NaHCO₃ and extracted with DCM (3X). The organic layers were combined, 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 EtOAc : petroleum ether (10-60%) to afford the title compound.

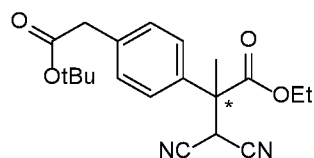
Step E- Ethyl 2-[4-(3-*tert*-butoxy-3-oxopropyl)-1-(4-methoxybenzyl)-1*H*-imidazol-2-yl]-3,3-dicyanoacrylate. To a flask containing *tert*-butyl 3-[2-(2-ethoxy-2-oxoacetyl)-1-(4-methoxybenzyl)-1*H*-imidazol-4-yl]propanoate (2.0 g, 4.80 mmol), malononitrile (1.59 g, 24.01 mmol) in chloroform (20 mL) at RT was added aluminium oxide (4.9 g, 48.0 mmol). The resulting mixture was stirred for 2 h at RT then filtered, and the residue rinsed with DCM. The
30 filtrate was diluted with aq. sat. NH₄Cl and extracted with DCM (3X). The organic layers were combined, 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 EtOAc : petroleum ether (10-60%) to afford the title compound.

Step F- Ethyl 2-{4-[3-(*tert*-butoxy)-3-oxopropyl]-1-(4-methoxybenzyl)-1*H*-imidazol-2-yl}-3,3-dicyano-2-methylpropanoate.

A flask, under an inert atmosphere of nitrogen, containing ethyl 2-{4-[3-(*tert*-butoxy)-3-oxopropyl]-1-(4-methoxybenzyl)-1*H*-imidazol-2-yl}-3,3-dicyanoacrylate (550 mg, 1.18 mmol) and lithium chloride (100 mg, 2.37 mmol) in THF (10 mL) was stirred 30 min at 0 °C before methylmagnesium chloride (0.51 mL, 1.54 mmol, 3M in THF) was added dropwise at 0 °C. The mixture was stirred for 2 h at 0 °C, then quenched by the addition of aq. sat. NH₄Cl 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 purified by silica gel column chromatography with EtOAc : petroleum ether (0-50%) to afford the title compound **I-77**. ¹H NMR (300 MHz, CDCl₃) δ 6.97 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.55 (s, 1H), 5.22 (s, 1H), 5.05 (s, 2H), 4.29-4.09 (m, 2H), 3.82 (s, 3H), 2.82 (t, *J* = 7.2 Hz, 2H), 2.58 (t, *J* = 7.2 Hz, 2H), 1.98 (s, 3H), 1.41 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 3H); *m/z* = 479 (*M* - 1).

INTERMEDIATE 78A

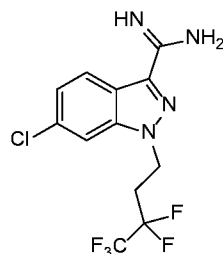
Ethyl 2-(4-(2-(*tert*-butoxy)-2-oxoethyl)phenyl)-3,3-dicyano-2-methylpropanoate



A microwave vial, under an inert atmosphere of nitrogen, containing **I-21A** (500 mg, 1.56 mmol), (2-(*tert*-butoxy)-2-oxoethyl)zinc(II) bromide (4.05 g, 15.57 mmol), tetrakis(dibenzylideneacetone)dipalladium (179 mg, 0.16 mmol) and tri-*tert*-butylphosphonium tetrafluoroborate (181 mg, 0.62 mmol) in THF (15 mL) was stirred for 1 h at RT and then irradiated with microwave radiation for 1 h at 120 °C. The reaction was quenched by the addition of aq. sat. NH₄Cl 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 purified by silica gel column chromatography with EtOAc : petroleum ether (0-20%) to afford the title compound **I-78A**. ¹H NMR (400 MHz, CD₃OD), 7.41-7.33 (m, 4H), 4.86 (s, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.57 (s, 2H), 1.93 (s, 3H), 1.42 (s, 9H), 1.23 (t, *J* = 7.2 Hz, 3H); *m/z* = 355 (*M* - 1).

INTERMEDIATE A1

6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazole-3-carboximidamide



Step A- 6-chloro-1H-indazole: Acetic anhydride (10.0 mL, 106 mmol) was added dropwise to a benzene solution (110 mL) containing 5-chloro-2-methylaniline (5.0 g, 35.3 mmol) and potassium acetate (3.8 g, 38.7 mmol) at RT. After 10 minutes the reaction mixture was heated to 80 °C. *tert*-butyl nitrite (6.99 mL, 90%, 53.0 mmol) was added over 20 minutes. The reaction mixture was kept at 80°C overnight, then cooled to RT and concentrated. The residue was dissolved in MeOH and stirred for 10 minutes. The solution was concentrated and to the residue was added MeOH (175 mL), THF (30 mL), water (60 mL) and LiOH monohydrate (8 g, 195 mmol). The solution was then stirred overnight at RT. The solution was then concentrated and the residue partitioned between EtOAc and 0.5 M NaOH aq. The aqueous phase was extracted with EtOAc (2X). The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated to give the indicated product. The material was used in Step B without further purification. ¹H NMR (400 MHz, CH₃CN-d₃): δ 11.20 (br s, 1H); 8.01 (s, 1H); 7.75-7.70 (m, 1H); 7.60 (s, 1H); 7.13 (dd, *J* = 8.6, 1.7 Hz, 1H). *m/z* = 153 (M+1).

Step A alternative- 6-chloro-1H-indazole. A DMA (250 mL) solution containing 4-chloro-2-fluorobenzaldehyde (50 g, 315 mmol) and hydrazine monohydrate (230 mL, 4730 mmol) was stirred for 30 minutes at RT. The solution was then stirred at 100 °C for 17 hours. The reaction mixture, which was a thick white slurry, was cooled to RT. The solid was collected by filtration, washed with water and dried under vacuum to give the title product.

Step B- 6-chloro-3-iodo-1H-indazole. An MeCN solution (250 mL) containing the intermediate from Step A (6.14 g, 40.2 mmol) and NIS (9.33g, 41.4 mmol) was heated at 60 °C for 3 hours. The reaction solution was cooled to RT and concentrated to approximately 70 mL volume. The reaction was then diluted with water, the suspension was stirred for 10 minutes and then filtered. The solid was air dried on the filter to give the indicated product. The material was used in Step C without further purification. ¹H NMR (400 MHz, CH₃CN-d₃): δ 1.52 (br s, 1 H); 7.62 (d, *J* = 1.7 Hz, 1H); 7.44 (d, *J* = 8.6 Hz, 1H); 7.21 (dd, *J* = 8.6, 1.7 Hz, 1H). *m/z* = 279.0 (M+1).

Step C- 6-chloro-1H-indazole-3-carbonitrile. A DMA (48 mL) solution containing the intermediate from Step B (4.0 g, 14.36 mmol), zinc powder (113 mg, 1.72 mmol), zinc cyanide (1.01 g, 8.86 mmol), 1,1'-bis(diphenylphosphino)ferrocene (318 mg, 0.58 mmol) and

tris(dibenzylideneacetone)dipalladium (263 mg, 0.29 mmol) was heated at 120 °C for 45 minutes. The solution was cooled to RT and partitioned between EtOAc and 0.5M HCl aq. The organic phase was washed twice with 0.5M aq. HCl and brine. The organic phase was then dried over MgSO₄, filtered and concentrated. The crude material was purified by silica gel

5 chromatography using a hexanes/EtOAc gradient to give the indicated product. ¹H NMR (400 MHz, CH₃CN-d₃): δ 7.83 (d, *J* = 8.7 Hz, 1H); 7.77 (d, *J* = 1.7 Hz, 1H); 7.36 (dd, *J* = 8.7, 1.7 Hz, 1H); *m/z* = 178.1 (M+1).

Step D- 6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazole-3-carbonitrile. An acetonitrile solution (450 mL) containing the intermediate from Step C (30 g, 169 mmol), potassium

10 carbonate (116.6 g, 844 mmol) and 1,1,1,2,2-pentafluoro-4-iodobutane (97.2 g, 354.7 mmol) was refluxed for 36 hours. The solution was cooled to RT and partitioned between EtOAc and water.

The organic phase was concentrated and the crude material was filtered through a plug of silica gel using 10% EtOAc/heptanes as the eluent. The isolated material was subsequently

15 recrystallized from heptanes to give the indicated product. ¹H NMR (400 MHz, CH₃CN-d₃): δ 7.87-7.80 (m, 2H); 7.40 (dd, *J* = 8.7, 1.7 Hz, 1H); 4.77 (t, *J* = 7.0 Hz, 2H); 2.95-2.78 (m, 2H). *m/z* = 324.1 (M+1).

Step E- 6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazole-3-carboximidamide.

Trimethylaluminum (23.17 mL, 46.3 mmol, 2.0 M in toluene) was added dropwise to a suspension of ammonium chloride (2.49 g, 46.5 mmol) in 69 mL toluene at 0 °C. The solution

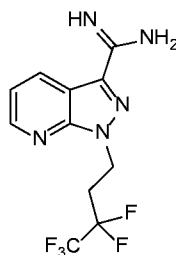
20 was stirred at RT for 3 hours, then added to the intermediate from Step D (3.0 g, 9.27 mmol) and heated at 110 °C for 6 hours. The mixture was cooled to RT and poured to a mixture of silica gel and MeOH. After stirring for 1.5 h the suspension was filtered and the filtrate concentrated to

give **I-A1**. ¹H NMR (400 MHz, CH₃CN-d₃): δ 8.26 (d, *J* = 8.7 Hz, 1H); 7.70 (d, *J* = 1.7 Hz, 1H); 7.24 (dd, *J* = 8.7, 1.8 Hz, 1H); 4.67 (t, *J* = 7.1 Hz, 2H); 3.01-2.78 (m, 2H); *m/z* = 341.1

25 (M+1).

INTERMEDIATE A2

1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboximidamide



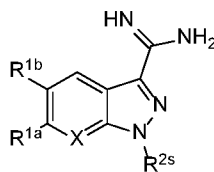
Step A- 1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-*b*]pyridine-3-carbonitrile. In a flask containing 1H-pyrazolo[3,4-*b*]pyridine-3-carbonitrile (5 g, 34.7 mmol) in acetonitrile (75 mL) was added 1,1,1,2,2-pentafluoro-4-iodobutane (9.82 mL, 69.4 mmol) and potassium carbonate (24.0 g, 173 mmol). 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 was purified by silica gel column chromatography with EtOAc:Hex (0-100%) to afford the title compound.

Step B- 1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-*b*]pyridine-3-carboximidamide

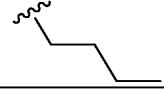
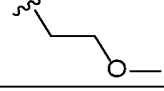
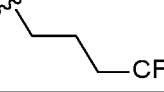
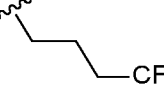
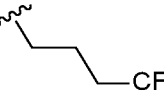
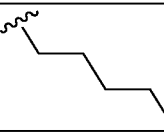
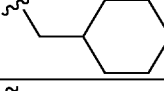
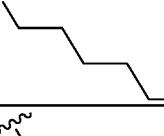
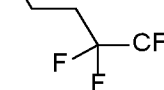
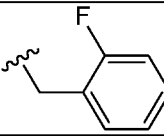
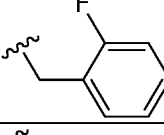
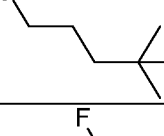
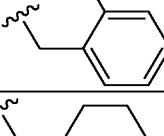
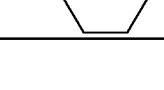
In a flask containing 1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-*b*]pyridine-3-carbonitrile (5.1 g, 17.7 mmol) in MeOH (11 mL) at RT was added NaOMe (1.34 g, 24.7 mmol). The mixture was stirred at RT for 3 h before acetic acid (4.05 mL, 70.7 mmol) was added, followed by ammonium chloride (1.23 g, 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 purified by silica gel column chromatography with (EtOAc:MeOH 10:1):hexane gradient to afford the title compound **I-A2**. 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).

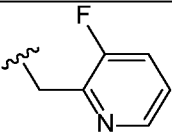
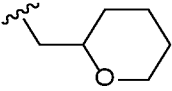
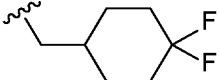
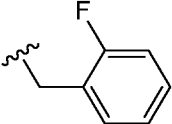
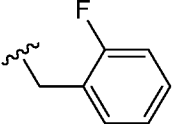
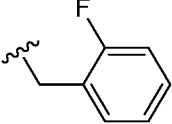
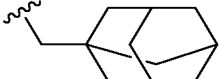
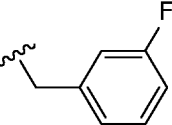
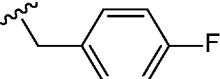
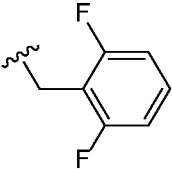
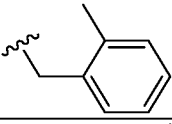
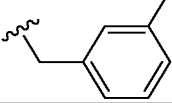
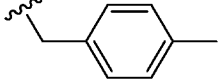
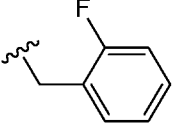
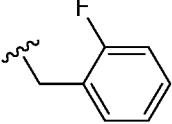
Using a similar procedure to that described in the preparation of Intermediate **A1** and **A2**, the following compounds in **Table 10** were prepared from commercial starting reagents or compounds known in the literature.

Table 10

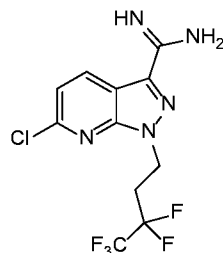


Int.	X	R2s	R1b	R1a	<i>m/z</i> (M+1)
I-A3	N		F	H	276
I-A4	N		F	H	326

I-A5	C(H)		H	Cl	251
I-A6	N		H	H	218
I-A7	C(H)		H	Cl	253
I-A8	C(H)		H	Cl	305
I-A9	N		H	H	272
I-A10	N		F	H	290
I-A11	C(H)		H	Cl	265
I-A12	C(H)		H	Cl	291
I-A13	C(H)		H	Cl	279
I-A14	C(H)		H	F	325
I-A15	C(H)		H	Cl	303
I-A16	N		H	H	270
I-A17	C(H)		H	Cl	293
I-A18	N		F	H	288
I-A19	C(H)		H	Cl	305

I-A20	C(H)		H	Cl	304
I-A21	C(H)		H	Cl	293
I-A22	C(H)		H	Cl	327
I-A23	C(H)		H	F	287
I-A24	C(H)		OMe	Cl	333
I-A25	C(H)		H	Me	283
I-A26	C(H)		H	Cl	343
I-A27	C(H)		H	Cl	303
I-A28	C(H)		H	Cl	303
I-A29	C(H)		H	Cl	321
I-A30	C(H)		H	Cl	299
I-A31	C(H)		H	Cl	299
I-A32	C(H)		H	Cl	299
I-A33	C(H)		F	H	287
I-A34	C(H)		Cl	H	303

INTERMEDIATE A35

6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-b]pyridine-3-carboximidamide

5 **Step A- 1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-b]pyridine-3-carbonitrile.** Using essentially the same procedures described in **I-A1** steps C and D, the title compound was prepared, using 3-iodo-1H-pyrazolo[3,4-b]pyridine as starting material. $m/z = 291$ (M+1).

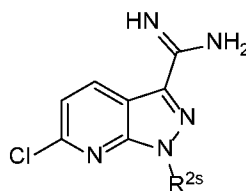
Step B- 3-cyano-1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-b]pyridine 7-oxide. In a flask containing 1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-b]pyridine-3-carbonitrile (6.3 g, 21.8 mmol) and 3-chloroperbenzoic acid (22 g, 98 mmol) was added acetic acid (50 mL). The
10 resulting mixture was stirred at 80 °C for 8 h before the mixture was cooled to RT and concentrated *in vacuo* to dryness. The residue was dissolved in 250 mL of a 2:1 mixture of Hexane : EtOAc and the pH was adjusted to pH 7 by addition of a sat. aq. K_2CO_3 . The resulting solution was extracted with EtOAc (3X) and the organic layers were combined, washed with
15 brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo* to dryness. The residue purified by silica gel chromatography with EtOAc : petroleum ether: NH_3 (2M in MeOH) (0-20%) to afford the title compound. $m/z = 307$ (M+1).

Step C- 6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-b]pyridine-3-carbonitrile. In a flask containing 3-cyano-1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-b]pyridine 7-oxide
20 (1.9 g, 1.2 mmol) was added Phosphorus (V) oxychloride (6.9 mL, 74 mmol). The resulting mixture was stirred at 80 °C for 5 h. The mixture was diluted in 250 mL of a 2:1 mixture of Hexane : EtOAc and the pH was adjusted to pH 7 by addition of a sat. aq. K_2CO_3 . The resulting solution was extracted with a 2:1 mixture of hexane : EtOAc (3X). The organic layers were combined, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo* to
25 dryness. The residue was purified by silica gel chromatography with EtOAc : petroleum ether to afford the title compound. $m/z = 325$ (M+1).

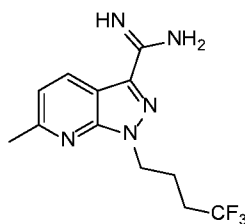
Step D- 6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-b]pyridine-3-carboximidamide. Trimethylaluminum (19.9 mL, 39.8 mmol, 2.0 M in toluene) was added dropwise to a suspension of ammonium chloride (2.1 g, 39.8 mmol) in 24 mL toluene at 0 °C.

The solution was then stirred at RT for 3 hours then added to 6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonitrile (2.6 g, 8.0 mmol) and heated at 75 °C overnight. The reaction mixture was cooled to RT, and quenched by the addition of MeOH:DCM (1:1) and silica. After stirring for 3 hours the suspension was filtered through
 5 diatomaceous earth and the filtrate was concentrated *in vacuo* dryness to afford the title compound **I-A35**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.68 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 6.68 (br, 3H), 4.76 (t, *J* = 7.2 Hz, 2H), 3.07-2.93 (m, 2H); *m/z* = 342 (M+1).

Using a similar procedure to that described in the preparation of Intermediate **I-A35**, the following compounds in **Table 7** were prepared from commercial starting reagents or
 10 compounds known in the literature.

Table 11

Int.	R2s	<i>m/z</i> (M+1)
I-A36		252
I-A37		306

INTERMEDIATE A38**6-Methyl-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboximidamide**

Step A- 6-chloro-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonitrile. Using essentially the same procedures described in intermediate **I-35** step A to C, the title compound was prepared. ¹H NMR (300 MHz, CDCl₃) δ 8.16 (d, *J* = 8.5 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H),
 20 4.65 (t, *J* = 6.6 Hz, 2H), 2.38 – 2.09 (m, 4H); *m/z* = 288 (M+1).

Step B- 6-methyl-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonitrile: To a solution containing 6-chloro-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonitrile

(800 mg, 2.77 mmol) in THF (10 mL) was added bis(triphenylphosphine)palladium(II) dichloride (195 mg, 0.28 mmol) the resulting solution was stirred at RT for 30 min.

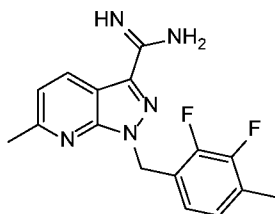
Dimethylzinc (8.31 mL, 8.31 mmol, 1 M in THF) was added and the resulting mixture was stirred 16 hours at RT. The reaction was quenched by the addition of aq. sat. NH_4Cl , extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc:petroleum ether (0-30%) to afford the title compound. $m/z = 269$ (M+1).

Step C- 6-methyl-1-(4,4,4-trifluorobutyl)-1H-pyrazolo[3,4-b]pyridine-3-carboximidamide.

Trimethylaluminum (4.0 mL, 8.0 mmol, 2.0 M in toluene) was added dropwise to a suspension of ammonium chloride (570 mg, 10.6 mmol) in 10 mL toluene cooled to 0 °C. The solution was then stirred at RT for 1 hours. To this solution was added 6-methyl-1-(4,4,4-trifluorobutyl)-1H-pyrazolo[3,4-b]pyridine-3-carbonitrile (270 mg, 1.00 mmol) and the resulting mixture was heated at 100 °C for 2 h. The reaction mixture was cooled to 0 °C, and quenched by the addition of a MeOH:DCM (1:1) mixture. After stirring for 1 hour the suspension was filtered through diatomaceous earth and the filtrate was concentrated *in vacuo* dryness. The residue was diluted in EtOAc and the pH was adjusted to pH 10 by addition of 1 M NaOH (aqueous solution). The resulting solution was extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo* to afford the title compound **I-A38**. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.50 (d, $J = 8.4$ Hz, 1H), 7.18 (d, $J = 8.4$ Hz, 1H), 6.48 (br, 3H), 4.52 (t, $J = 7.2$ Hz, 2H), 2.61 (s, 3H), 2.45-2.28 (m, 2H), 2.16-2.06 (m, 2H); $m/z = 286$ (M+1).

INTERMEDIATE A39

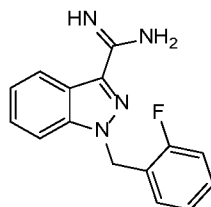
1-(2,3-difluoro-4-methylbenzyl)-6-methyl-1H-pyrazolo[3,4-b]pyridine-3-carboximidamide



The title compound was prepared using the protocol published in WO 2015-004105-A1.

INTERMEDIATE A40

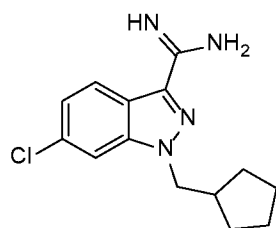
1-(2-fluorobenzyl)-1H-indazole-3-carboximidamide



A flask under nitrogen containing **I-A15** (1.0 g, 2.95 mmol) and palladium on carbon (1.0 g, 10w%) in MeOH (50 mL), was purged with hydrogen. The mixture was stirred at RT for 0.5 h under an atmosphere of hydrogen (~2 atm). The solid was filtered out and washed with MeOH (3X). The filtrate was concentrated *in vacuo* to dryness. The residue was purified by C18 column chromatography with acetonitrile:water:0.1% trifluoroacetic acid, (20%-40%) to afford the title compound **I-A40**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.40-9.30 (br, 4H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.64-7.59 (m, 1H), 7.47-7.37 (m, 2H), 7.28-7.23 (m, 2H), 7.21-7.16 (m, 1H), 5.92 (s, 2H); *m/z* = 269 (M+1).

INTERMEDIATE A41

6-Chloro-1-(cyclopentylmethyl)-1H-indazole-3-carboximidamide



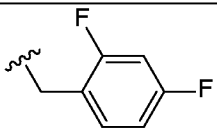
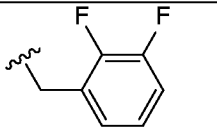
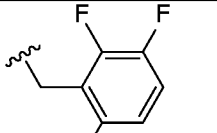
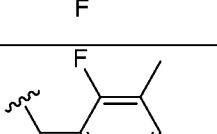
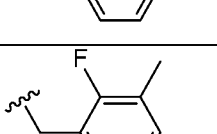
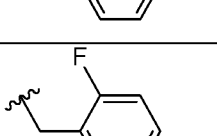
Step A- 6-Chloro-1-(cyclopentylmethyl)-1H-indazole-3-carbonitrile. To a flask containing 6-chloro-1H-indazole-3-carbonitrile (1.0 g, 5.63 mmol) and cyclopentylmethyl 4-methylbenzenesulfonate (1.9 g, 7.32 mmol) in DMF (10 mL), was added potassium phosphate (2.4 g, 11.26 mmol) and the resulting mixture was stirred for 16 h at 70 °C. The reaction was cooled to RT, quenched by the addition of brine, and 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 EtOAc:petroleum ether (0-10%) to afford the title compound. *m/z* = 301 (M+1).

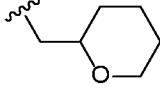
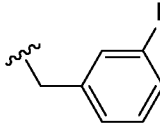
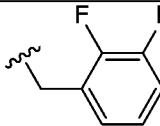
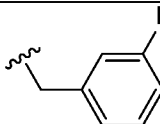
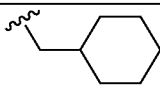
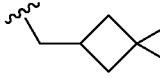
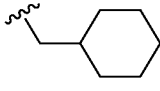
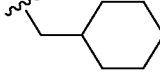
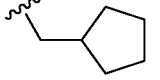
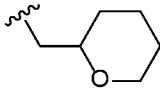
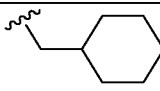
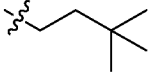
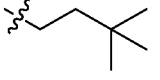
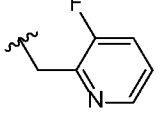
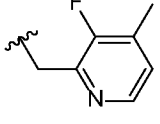
Step B- 6-Chloro-1-(cyclopentylmethyl)-1H-indazole-3-carboximidamide. To a flask, under a inert atmosphere of nitrogen, containing 6-chloro-1-(cyclopentylmethyl)-1H-indazole-3-carbonitrile (1.0 g, 3.85 mmol) in MeOH (10 mL) was added NaOMe (0.42 g, 7.70 mmol). The solution was stirred for 2 h at RT and ammonium chloride (0.62 g, 11.55 mmol) was added. The resulting mixture was stirred for 3 h at 7 °C. The mixture was cooled to RT and concentrated *in vacuo* to dryness. The residue was poured into water (100 mL). 2N HCl solution was added to reach pH 1~2, the resulting solution was extracted with Et₂O (2 X) and the aqueous layer was

5

10

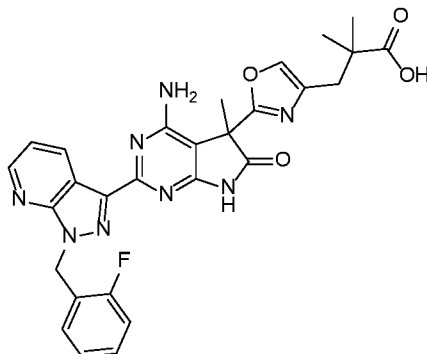
N#CC(=N)N1C(=N2C(=C(C=C2)C(=C1)C(=C(C=C2)R1a)C(=C(C=C2)R1b)X)N(C2)R2s

Int.	X	R2s	R1b	R1a	<i>m/z</i> (M+1)
I-A42	C(H)		H	Cl	321
I-A43	C(H)		H	Cl	321
I-A44	C(H)		H	Cl	339
I-A45	C(H)		H	Cl	317
I-A46	C(H)		H	F	301
I-A47	C(H)		H	Cl	317

I-A48	C(H)		H	F	277
I-A49	C(H)		H	F	287
I-A50	C(H)		H	F	305
I-A51	N		H	H	270
I-A52	N		H	H	258
I-A53	C(H)		H	Cl	299
I-A54	C(H)		H	F	275
I-A55	C(H)		H	F	289
I-A56	N		H	H	244
I-A57	N		H	H	260
I-A58	N		H	H	272
I-A59	N		H	H	246
I-A60	C(H)		H	Cl	279
I-A61	C(H)		H	H	270
I-A62	C(H)		H	Cl	318

EXAMPLE 1A

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



- 5 **Step A- methyl 3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoate.** Into a flask was placed **I-A16** (200 mg, 0.74 mmol), **I-32** (258 mg, 0.74 mmol), potassium bicarbonate (112 mg, 1.11 mmol) and *t*-BuOH (10 mL). The resulting mixture was stirred at 80 °C for 16 h then concentrated *in vacuo* to dryness. The residue was purified by
- 10 silica gel chromatography using (MeOH : DCM) to afford the racemic title product. The racemic material was resolved using Chiral SFC (CHIRALPAK[®] AD-H) to afford isomer **A** (faster eluting) and isomer **B** (slower eluting). *m/z* = 571 (M+1).
- Step B- 3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid.**
- 15 To a flask containing methyl 3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoate isomer **A** (160 mg, 0.280 mmol) in MeOH (5 mL) was added LiOH (67 mg, 2.80 mmol) in 1 mL of water. The resulting mixture was stirred 48 h at RT. The reaction was concentrated *in vacuo* to dryness. The residue was diluted with concentrated sat. Na₂CO₃ and
- 20 extracted with EtOAc (3X). The pH of the aqueous phase was adjusted to pH 6 with HCl (1M) the resulting solid was collected by filtration, washed with water, and dried under vacuum to afford the title product **Ex-1A**. ¹H NMR (300 MHz, CD₃OD) δ 9.06 (d, *J* = 7.8 Hz, 1H), 8.61 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.63 (s, 1H), 7.40-7.27 (m, 2H), 7.16-7.06 (m, 3H), 5.91 (s, 2H), 2.86-2.72(m, 2H), 1.92 (s, 3H), 1.23 (s, 3H), 1.19 (s, 3H); *m/z* = 557 (M + 1).
- 25 Using essentially the same procedure described in **Ex-1A**, the following compounds in **Table 13** were prepared.

Table 13

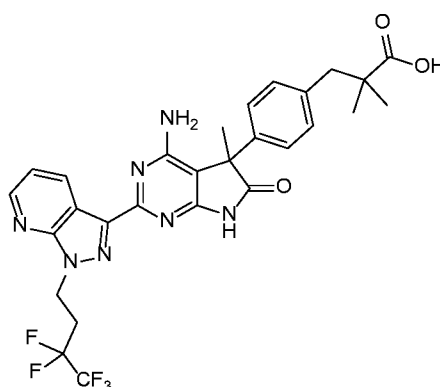
Ex.	Int. SM	Chiral Resolution Column	Structure	Name	<i>m/z</i> (M+1)
2A	I-32	IA		3-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid	628
3A	I-32	IA		3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid	590
4B	I-14	(R,R)WHE LK-01		3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-bromophenyl)propanoic acid	689
5BA	I-11B	IA		(5S)-3-{4-[4-amino-2-{6-chloro-1-[(4-methylcyclohexyl)methyl]-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl}propanoic acid	573
5BB	I-11B	IA		(5S)-3-{4-[4-amino-2-{6-chloro-1-[(4-methylcyclohexyl)methyl]-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl}propanoic acid	573

6BA	I-11B	IC		(5 <i>S</i>)-3-{4-[4-amino-2-{6-chloro-1-[tetrahydro-2 <i>H</i> -pyran-2-ylmethyl]-1 <i>H</i> -indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl}propanoic acid	561
7A	I-11	AD		(<i>S</i>)-3-(4-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoic acid	576
8B	I-20	IC		3-(6-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}pyridin-3-yl)-2,2-dimethylpropanoic acid	638
¹H NMR Data					
2A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.23 (s, 1H), 11.39 (s, 1H), 8.68 (d, <i>J</i> = 8.7 Hz, 1H), 8.04 (d, <i>J</i> = 1.7 Hz, 1H), 7.75 (s, 1H), 7.28 (dd, <i>J</i> = 8.7, 1.7 Hz, 1H), 6.65 (s, 2H), 4.84 (t, <i>J</i> = 6.9 Hz, 2H), 2.91 (tt, <i>J</i> = 19.4, 6.9 Hz, 2H), 2.76 – 2.56 (m, 2H), 1.81 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H)				
3A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.22 (s, 1H), 11.37 (s, 1H), 8.69 (d, <i>J</i> = 8.7 Hz, 1H), 8.01 (d, <i>J</i> = 1.7 Hz, 1H), 7.74 (s, 1H), 7.42 – 7.11 (m, 5H), 6.64 (s, 2H), 5.81 (s, 2H), 2.71 – 2.57 (m, 2H), 1.80 (s, 3H), 1.09 (d, <i>J</i> = 8.7 Hz, 6H)				
4B	¹ H NMR (300 MHz, CD ₃ OD) δ 8.70 (d, <i>J</i> = 8.7 Hz, 1H), 7.77 (s, 1H), 7.56 (d, <i>J</i> = 1.8 Hz, 1H), 7.41-7.21 (m, 3H), 4.83 (t, <i>J</i> = 7.2 Hz, 2H), 3.12-2.84 (m, 4H), 2.66-2.45 (m, 2H), 1.87 (s, 3H)				
5BA	¹ H NMR (300 MHz, CD ₃ OD) δ 8.66 (d, <i>J</i> = 9.0 Hz, 1H), 7.70 (s, 1H), 7.34-7.21 (m, 5H), 4.42 (d, <i>J</i> = 7.5 Hz, 2H), 2.91 (t, <i>J</i> = 7.5 Hz, 2H), 2.59 (t, <i>J</i> = 7.5 Hz, 2H), 2.33-2.21 (m, 1H), 1.87 (s, 3H), 1.69-1.67 (m, 1H), 1.55-1.43 (m, 8H), 1.00 (d, <i>J</i> = 6.9 Hz, 3H)				
5BB	¹ H NMR (300 MHz, CD ₃ OD) δ 8.66 (d, <i>J</i> = 8.7 Hz, 1H), 7.69 (s, 1H), 7.31-7.21 (m, 5H), 4.31 (d, <i>J</i> = 7.2 Hz, 2H), 2.91 (t, <i>J</i> = 7.5 Hz, 2H), 2.57 (t, <i>J</i> = 7.5 Hz, 2H), 2.09-1.95 (m, 1H), 1.87 (s, 3H), 1.72-1.69 (m, 2H), 1.61-1.57 (m, 2H), 1.43-1.29 (m, 1H), 1.21-1.09 (m, 2H), 0.96-0.88 (m, 5H)				
6BA	¹ H NMR (300 MHz, CD ₃ OD) δ 8.61 (d, <i>J</i> = 8.7 Hz, 1H), 7.68 (d, <i>J</i> = 0.9 Hz, 1H), 7.30-7.17 (m, 5H), 4.52-4.38 (m, 2H), 3.88-3.84 (m, 2H), 3.36-3.28 (m, 1H), 2.88 (t, <i>J</i> = 7.5 Hz, 2H), 2.55 (t, <i>J</i> = 7.5 Hz, 2H), 1.89-1.80 (m, 4H), 1.68-1.64 (m, 1H), 1.57-1.30 (m, 4H)				

7A	¹ H NMR (500 MHz, CD ₃ OD) δ 9.07 (dd, <i>J</i> = 8.1, 1.6 Hz, 1H), 8.64 (dd, <i>J</i> = 4.6, 1.6 Hz, 1H), 7.38 (dd, <i>J</i> = 8.1, 4.6 Hz, 1H), 7.35 – 7.21 (m, 4H), 4.98 (t, <i>J</i> = 7.3 Hz, 2H), 3.01 (td, <i>J</i> = 18.4, 9.2 Hz, 2H), 2.93 (t, <i>J</i> = 7.6 Hz, 2H), 2.61 (t, <i>J</i> = 7.6 Hz, 2H), 1.90 (s, 3H)
8B	¹ H NMR (CD ₃ OD, 300 MHz) δ 8.60 (d, <i>J</i> = 9.0 Hz, 1H), 8.45 (s, 1H), 7.84 (s, 1H), 7.71 (dd, <i>J</i> = 8.1, 2.1 Hz, 1H), 7.49 (d, <i>J</i> = 8.4 Hz, 1H), 7.32 (dd, <i>J</i> = 8.7, 1.5 Hz, 1H), 4.88-4.83 (m, 2H), 3.09-2.87 (m, 4H), 1.93 (s, 3H), 1.20 (s, 6H)

EXAMPLE 9B

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



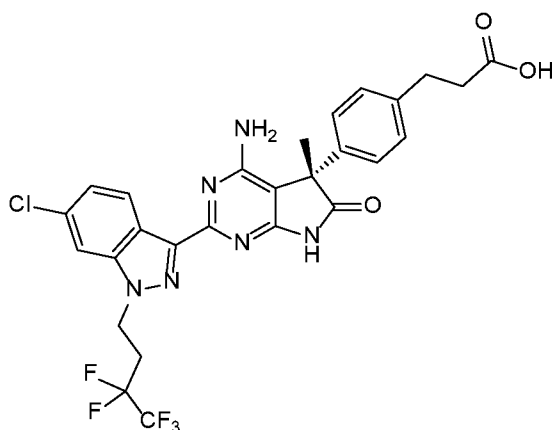
Step A- methyl 3-(4-{4-amino-5-methyl-6-oxo-2-(1-(3,3,4,4,4-pentafluorobutyl)-2,3-dihydro-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoate. Into a flask was placed **I-13B** (50 mg, 0.14 mmol), **I-A2** (48 mg, 0.14 mmol), potassium bicarbonate (42 mg, 0.42 mmol) and *t*-BuOH (1.4 mL). The resulting mixture was warmed at 65 °C for 16 h. The reaction was cooled to RT and quenched by the addition of water. The resulting solution was extracted with EtOAc (3X) 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 chromatography using (EtOAc: EtOH 3:1):hexane gradient to afford the title product. *m/z* = 618.2 (M+1).

Step B- 3-(4-{4-amino-5-methyl-6-oxo-2-(1-(3,3,4,4,4-pentafluorobutyl)-2,3-dihydro-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid. Into a flask was placed methyl 3-(4-{4-amino-5-methyl-6-oxo-2-(1-(3,3,4,4,4-pentafluorobutyl)-2,3-dihydro-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoate (61 mg, 0.10 mmol), LiOH (24 mg, 0.98 mmol), dioxane (2.5 mL) and water (2.5 mL). The resulting mixture was warmed at 65 °C for 16 h. The reaction was cooled to RT and quenched by the addition of acetic acid (73 μL, 1.3 mmol). The resulting solution was extracted with EtOAc (3X), the organic layers were

combined, dried over anhydr. MgSO_4 , filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using (EtOAc: EtOH 3:1):hexane gradient to afford the title product **Ex-9B**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.24 (s, 1H), 11.11 (s, 1H), 9.03 (dd, $J = 8.1, 1.6$ Hz, 1H), 8.63 (dd, $J = 4.5, 1.6$ Hz, 1H), 7.37 (dd, $J = 8.1, 4.5$ Hz, 1H), 7.17 (d, $J = 8.4$ Hz, 2H), 7.11 (d, $J = 8.3$ Hz, 2H), 6.56 (s, 2H), 4.87 (t, $J = 6.8$ Hz, 2H), 2.97 (tt, $J = 19.1, 6.8$ Hz, 2H), 2.74 (s, 2H), 1.77 (s, 3H), 1.04 (s, 6H); $m/z = 604$ (M+1)

EXAMPLE 10B

(S)-3-(4-{4-Amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid



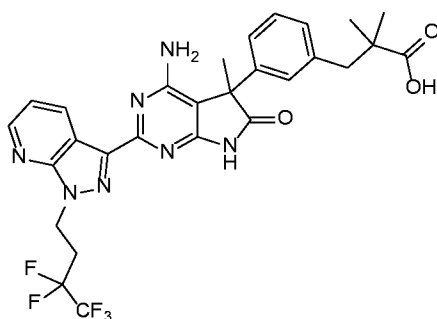
Step A- (S)-Methyl 3-(4-{4-Amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoate. In a flask containing **I-A1** (91 mg, 0.27 mmol), **I-11B** (80 mg, 0.24 mmol) and potassium bicarbonate (73.2 mg, 0.73 mmol) in *t*-BuOH (2.4 mL) was stirred at 80 °C for 16h. The reaction was cooled to RT, diluted with EtOAc and water, and extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography with (EtOAc:EtOH 3:1):hexane (0-40%) to afford the title compound. $m/z = 623$ (M+1).

Step B- (S)-3-(4-{4-Amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid. In a flask containing (S)-methyl 3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoate (120 mg, 0.19 mmol) in dioxane (8.7 mL) was added LiOH (46 mg, 1.93 mmol) in water (1 mL). The reaction was stirred 2 h at 50 °C. The reaction was cooled to RT, concentrated *in vacuo* and diluted with EtOAc. Acetic acid (132 μl , 2.31 mmol) was added and the mixture was extracted with EtOAc (3X). The organic layers were combined, washed with brine (2X), dried

over anhydr. MgSO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with (EtOAc:EtOH 3:1) : hexane (0-100%) to afford the title compound **Ex-10B**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.12 (s, 1H), 11.09 (s, 1H), 8.69 (d, $J = 8.7$ Hz, 1H), 8.03 (d, $J = 1.7$ Hz, 1H), 7.26 (dd, $J = 8.7, 1.7$ Hz, 1H), 7.22 – 7.11 (m, 4H), 6.54 (s, 2H), 4.82 (t, $J = 6.8$ Hz, 2H), 2.90 (tt, $J = 19.4, 6.9$ Hz, 2H), 2.77 (t, $J = 7.6$ Hz, 2H), 2.52 – 2.49 (m, 2H), 1.76 (s, 3H); $m/z = 609$ (M+1).

EXAMPLE 11B

3-(3-{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}phenyl)-2,2-dimethylpropanoic acid



Step A- methyl 3-(3-{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}phenyl)-2,2-dimethyl propanoate. To a flask containing intermediate **A2** (45.6 mg, 0.15 mmol) and **I-39B** (50 mg, 0.14 mmol) in THF (2.7 mL) was added triethylamine (56 μl , 0.40 mmol). The resulting mixture was stirred at 80 °C for 6 h then 24 h at 60 °C. The reaction was cooled to RT diluted with EtOAc and water. The resulting mixture was extracted with EtOAc (3X), the organic layers were combined, washed with brine, dried over anhydr. MgSO_4 , filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using (EtOAc:EtOH 3:1):hexane (0-40%) to afford the title compound. $m/z = 632$ (M+1).

Step B- 3-(3-{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}phenyl)-2,2-dimethylpropanoic acid. To a flask containing methyl 3-(3-{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}phenyl)-2,2-dimethyl propanoate (80 mg, 0.13 mmol) in a dioxane (5.8 mL) water (0.6 mL) mixture was added LiOH (30 mg, 1.28 mmol) the resulting mixture was stirred at 80 °C for 16 h. The reaction was cooled to RT, diluted with EtOAc and water, and quenched by the addition of acetic acid (87 μl , 1.52 mmol). The resulting solution was extracted with EtOAc

(3X) and the organic layers were combined, washed with brine dried over anhydr. MgSO_4 ,

filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using (EtOAc:EtOH 3:1):hexane (10%-70%) to afford the title compound

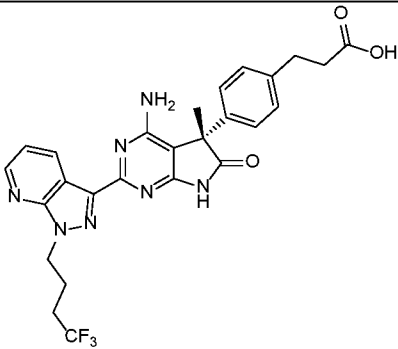
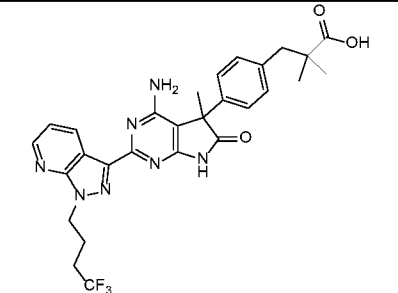
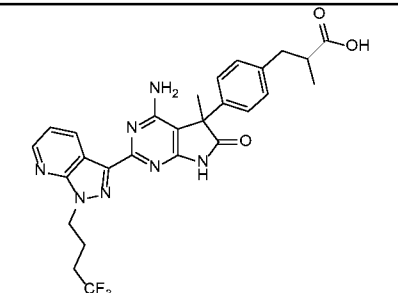
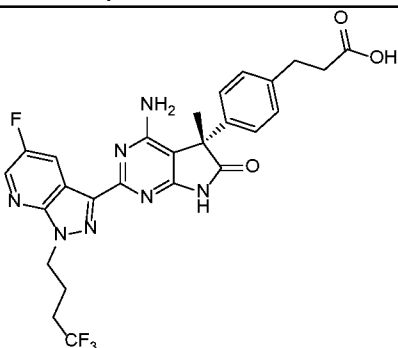
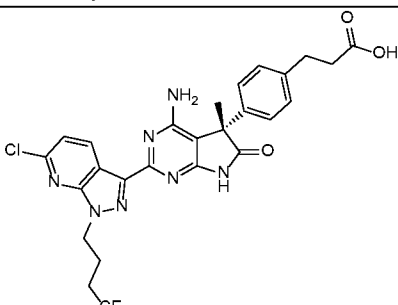
Ex-11B. ^1H NMR (500 MHz, MeOD) δ 9.03 (dd, $J = 8.1, 1.6$ Hz, 1H), 8.60 (dd, $J = 4.5, 1.6$ Hz, 1H), 7.35 (dd, $J = 8.1, 4.5$ Hz, 1H), 7.30 – 7.18 (m, 3H), 7.18 – 7.11 (m, 1H), 4.95 (t, $J = 7.3$ Hz, 2H), 3.05 - 2.93 (m, 2H), 2.91 (d, $J = 13.2$ Hz, 1H), 2.79 (d, $J = 13.2$ Hz, 1H), 1.88 (s, 3H), 1.18 (s, 3H), 1.10 (s, 3H); $m/z = 604$ (M+1).

Using essentially the same procedure described in examples 9, 10 and 11, the following

compounds in **Table 14** were prepared.

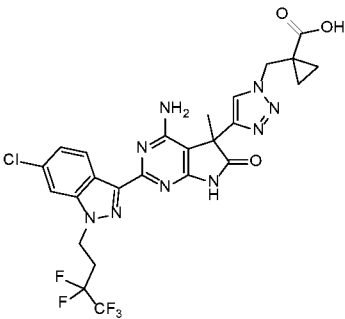
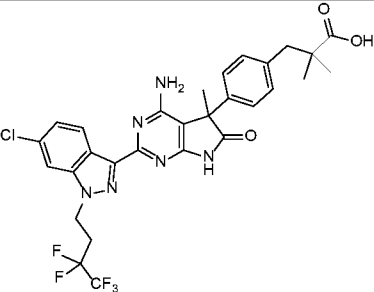
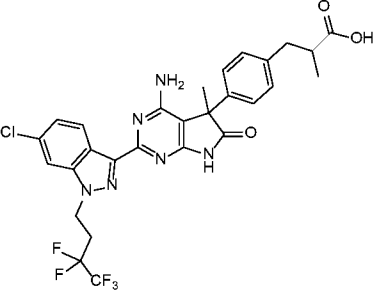
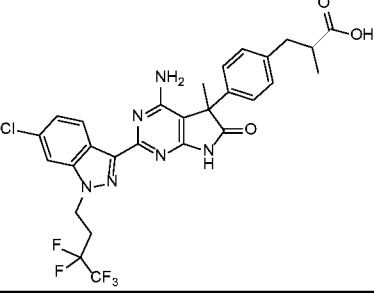
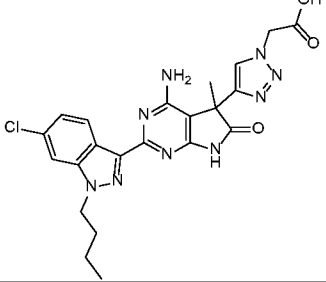
Table 14

Ex.	Int. SM	Structure	Name	m/z (M+1)
12B	I-24B		3-(4-{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}-1H-1,2,3-triazol-1-yl)propanoic acid	567
13B	I-11B		(S)-3-(4-{4-amino-2-(1-butyl-6-chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	520
14B	I-11B		(S)-3-(4-{4-amino-2-(1-butyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	486

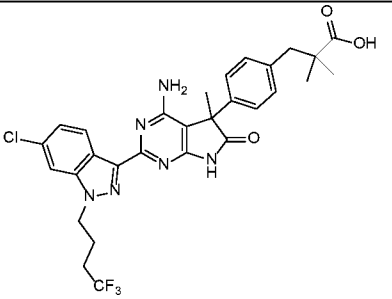
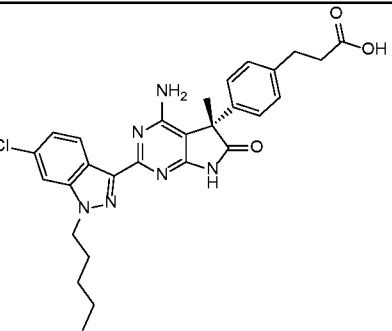
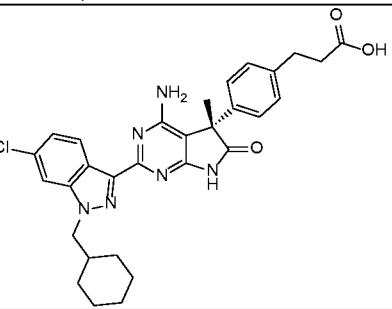
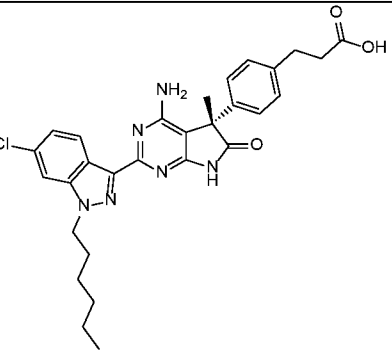
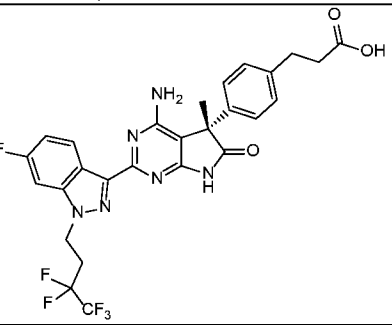
15B	I-11B		(<i>S</i>)-3-(4-{4-amino-5-methyl-6-oxo-2-[1-(4,4,4-trifluorobutyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoic acid	540
16B	I-13B		3-(4-{4-amino-5-methyl-6-oxo-2-[1-(4,4,4-trifluorobutyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid	568
17AB	I-38AB		3-(4-{4-amino-5-methyl-6-oxo-2-[1-(4,4,4-trifluorobutyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)-2-methylpropanoic acid	554
18B	I-11B		(<i>S</i>)-3-(4-{4-amino-2-[5-fluoro-1-(4,4,4-trifluorobutyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoic acid	558
19B	I-11B		(<i>S</i>)-3-(4-{4-amino-2-[6-chloro-1-(4,4,4-trifluorobutyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoic acid	574

20B	I-11B		(S)-3-(4-{4-amino-5-methyl-2-[6-methyl-1-(4,4,4-trifluorobutyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	554
21B	I-11B		(S)-3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	538
22A	I-15A		3-(3-{4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	538
23B	I-11B		(S)-3-(4-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	556
24A	I-15A		3-(3-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	556
25B	I-11B		(S)-3-(4-{4-amino-2-[1-(2,3-difluoro-4-methylbenzyl)-6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	584

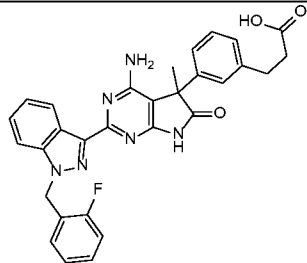
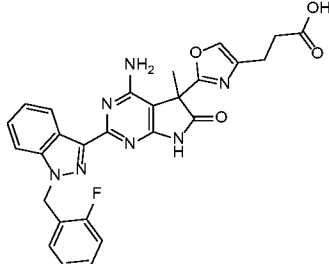
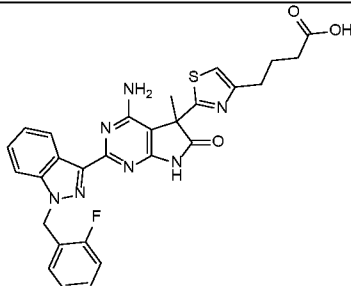
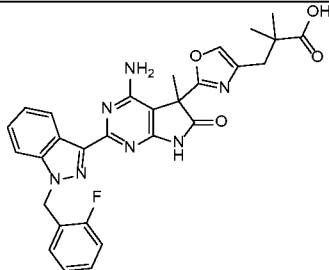
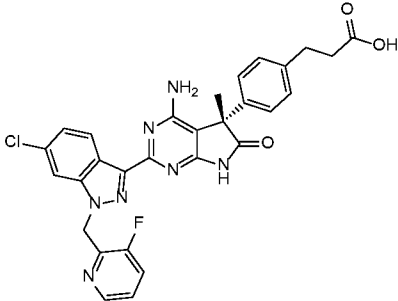
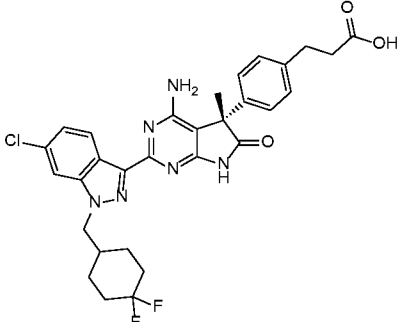
26B	I-37B		3-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}benzoic acid	581
27B	I-39B		3-(3-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid	638
28B	I-25B		(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1 <i>H</i> -1,2,3-triazol-1-yl)acetic acid	586
29B	I-24B		3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1 <i>H</i> -1,2,3-triazol-1-yl)propanoic acid	600
30B	I-26B		2-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1 <i>H</i> -1,2,3-triazol-1-yl)-2-methylpropanoic acid	614
31B	I-27B		3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1 <i>H</i> -1,2,3-triazol-1-yl)-2,2-dimethylpropanoic acid	628

32B	I-28B		1-[(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1 <i>H</i> -1,2,3-triazol-1-yl)methyl]cyclopropanecarboxylic acid	626
33B	I-13B		3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid	637
34AA	I-38AA		3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)-2-methylpropanoic acid	623
34AB	I-38AB		3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)-2-methylpropanoic acid	623
35B	I-25B		2-{4-[4-amino-2-(1-butyl-6-chloro-1 <i>H</i> -indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1 <i>H</i> -1,2,3-triazol-1-yl}acetic acid	496

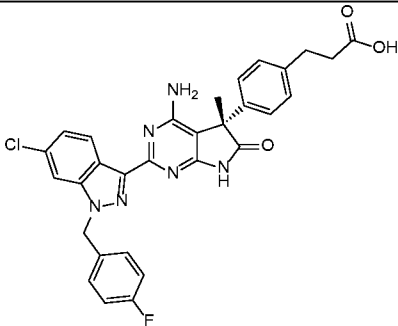
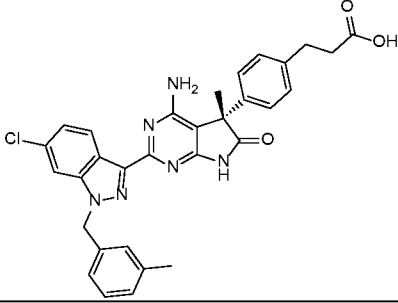
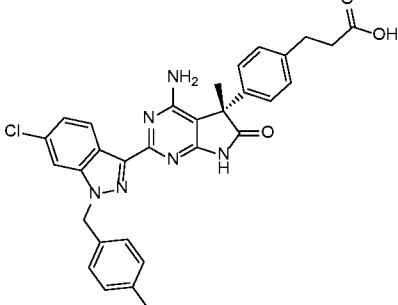
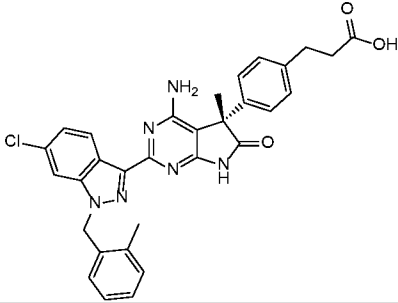
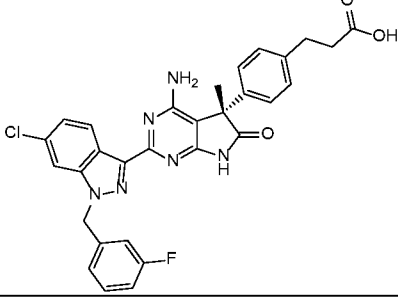
36B	I-24B		3-{4-[4-amino-2-(1-butyl-6-chloro-1 <i>H</i> -indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1 <i>H</i> -1,2,3-triazol-1-yl}propanoic acid	510
37B	I-13B		3-{4-[4-amino-2-(1-butyl-6-chloro-1 <i>H</i> -indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]phenyl}-2,2-dimethylpropanoic acid	547
38B	I-11B		(<i>S</i>)-3-{4-[4-amino-2-(1-butyl-6-chloro-1 <i>H</i> -indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]phenyl}propanoic acid	519
39B	I-39B		3-(3-{4-amino-2-[6-chloro-1-(2-methoxyethyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid	549
40B	I-11B		(<i>S</i>)-3-(4-{4-amino-2-[6-chloro-1-(2-methoxyethyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoic acid	521
41B	I-11B		(<i>S</i>)-3-(4-{4-amino-2-[6-chloro-1-(4,4,4-trifluorobutyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoic acid	573

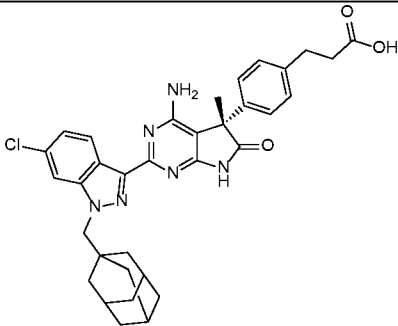
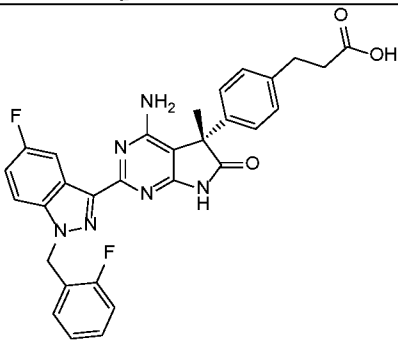
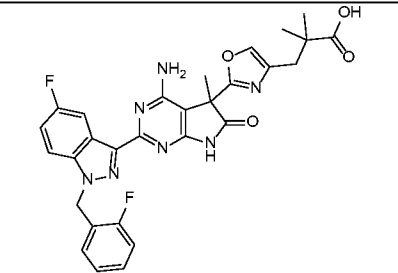
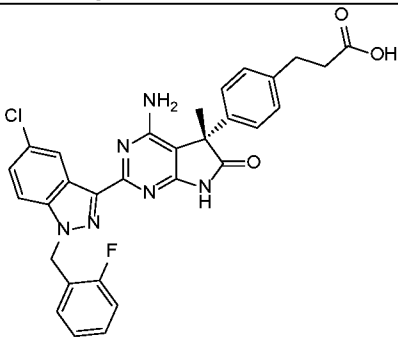
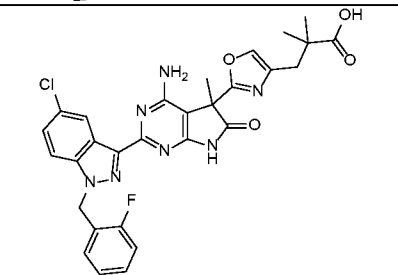
42B	I-13B		3-(4-{4-amino-2-[6-chloro-1-(4,4,4-trifluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid	601
43B	I-11B		(S)-3-{4-[4-amino-2-(6-chloro-1-pentyl-1H-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl}propanoic acid	533
44B	I-11B		(S)-3-(4-{4-amino-2-[6-chloro-1-(cyclohexylmethyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	559
45B	I-11B		(S)-3-{4-[4-amino-2-(6-chloro-1-hexyl-1H-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl}propanoic acid	547
46B	I-11B		(S)-3-(4-{4-amino-2-[6-fluoro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	593

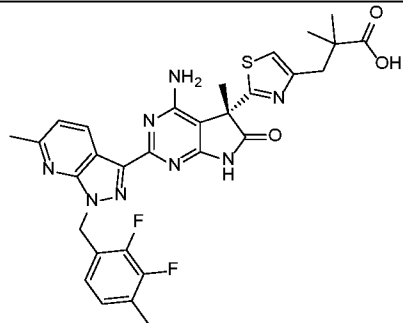
47B	I-11B		(S)-3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	571
48A	I-15A		3-(3-{4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	571
49A	I-36A		4-(2-{4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}thiazol-4-yl)butanoic acid	592
50A	I-33A		3-(2-{4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}oxazol-4-yl)propanoic acid	562
51B	I-34B		2-(2-{4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}oxazol-4-yl)acetic acid	548
52B	I-11B		(S)-3-(4-{4-amino-2-[6-chloro-1-(4,4-dimethylpentyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	561

53A	I-15A		3-(3-{4-amino-2-[1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoic acid	537
54A	I-33A		3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}oxazol-4-yl)propanoic acid	528
55A	I-36A		4-(2-{4-amino-2-[1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}thiazol-4-yl)butanoic acid	558
56A	I-42A		3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid	556
57B	I-11B		(<i>S</i>)-3-(4-[4-amino-2-{6-chloro-1-[(3-fluoropyridin-2-yl)methyl]-1 <i>H</i> -indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoic acid	572
58B	I-11B		(<i>S</i>)-3-(4-[4-amino-2-{6-chloro-1-[(4,4-difluorocyclohexyl)methyl]-1 <i>H</i> -indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoic acid	595

59B	I-11B		(<i>S</i>)-3-(4-{4-amino-2-[1-(2-fluorobenzyl)-6-methyl-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoic acid	551
60B	I-11B		(<i>S</i>)-3-(4-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoic acid	555
61A	I-15A		3-(3-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoic acid	555
62A	I-35A		(<i>S</i>)-3-(2-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid	590
63A	I-42A		3-(2-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid	574
64B	I-11B		(<i>S</i>)-3-(4-{4-amino-2-[6-chloro-1-(2,6-difluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoic acid	589

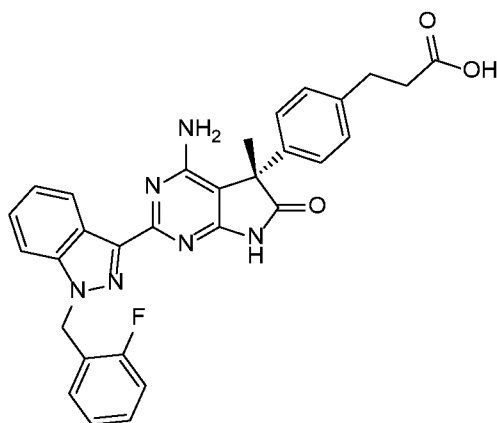
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66B	I-11B		(S)-3-(4-{4-amino-2-[6-chloro-1-(3-methylbenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	567
67B	I-11B		(S)-3-(4-{4-amino-2-[6-chloro-1-(4-methylbenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	567
68B	I-11B		(S)-3-(4-{4-amino-2-[6-chloro-1-(2-methylbenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	567
69B	I-11B		(S)-3-(4-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	571

70B	I-11B		(S)-3-(4-{2-[1-(adamantan-1-ylmethyl)-6-chloro-1H-indazol-3-yl]-4-amino-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	611
71B	I-11B		(S)-3-(4-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	555
72A	I-42A		3-(2-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid	574
73B	I-11B		(S)-3-(4-{4-amino-2-[5-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	571
74A	I-42A		3-(2-{4-amino-2-[5-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid	590

75A	I-43A		(S)-3-(2-{4-amino-2-[1-(2,3-difluoro-4-methylbenzyl)-6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}thiazol-4-yl)-2,2-dimethylpropanoic acid	619
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EXAMPLE 76B

(S)-3-(4-{4-Amino-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid



5

Step A- (S)-methyl 3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoate. The title compound was prepared using essentially the same procedures described in Example 11 Step A, using intermediate I-A15 and I-11B as starting material.

10 **Step B- (S)-methyl 3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoate.** A flask under nitrogen, containing (S)-methyl 3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoate (100 mg, 0.17 mmol) and palladium on carbon (50 mg, 10 wt%) in MeOH (8 mL) was purged with hydrogen. The mixture was stirred at RT for 6 h under an atmosphere of hydrogen (~2 atm). The solid was filtered out and washed with MeOH (3X). The filtrate was concentrated *in vacuo* to dryness.

15 The residue was purified by silica gel column chromatography with MeOH:DCM (0-10%) to afford the title compound. $m/z = 551$ (M+1).

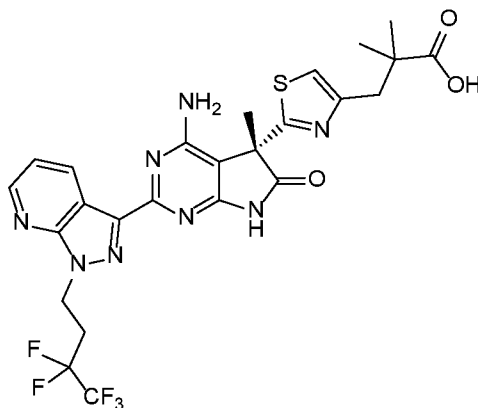
Step C- (S)-3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid. To a flask containing (S)-

20

methyl 3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoate (80 mg, 0.145 mmol) in MeOH (5 mL) was added LiOH (35 mg, 1.45 mmol) in 1 mL of water. The resulting mixture was stirred for 16 h at RT before been concentrated *in vacuo*. The residue was diluted with hydrochloric acid (14.5 mL, 0.1 N), the solid was collected by filtration, washed with water and dried *in vacuo*. The residue was then purified by reverse phase HPLC (ACN/water with 0.05% TFA modifier) to afford the title compound **Ex-76B**. ¹H NMR (400 MHz, CD₃OD) δ 8.63 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.57 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.45-7.28 (m, 6H), 7.22-7.11 (m, 3H), 5.92 (s, 2H), 2.93 (t, *J* = 7.2 Hz, 2H), 2.61 (t, *J* = 7.2 Hz, 2H), 1.95 (s, 3H); *m/z* = 537 (*M* + 1).

EXAMPLE 77B

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



Step A- (*S*)-ethyl 4-amino-5-methyl-6-oxo-2-(1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxylate. To a mixture of **I-A2** (1.0g, 3.2 mmol) and **I-40B** (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 and 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 B- (*S*)-4-amino-5-methyl-6-oxo-2-(1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide. In a sealed tube containing (*S*)-ethyl 4-amino-5-methyl-6-oxo-2-(1-(3,3,4,4,4-pentafluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-6,7-dihydro-5*H*-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 and 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 C- (S)-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 (S)-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 D- (S)-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 (S)-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 and 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 E- (S)-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-

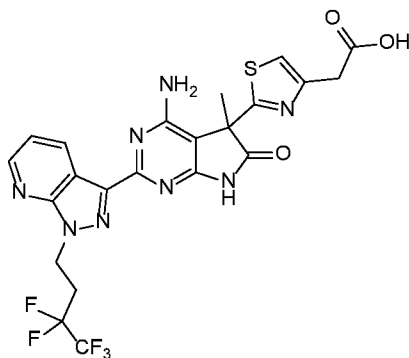
dimethylpropanoic acid. Into a flask was placed (S)-ethyl 3-(2-(4-amino-5-methyl-6-oxo-2-(1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)thiazol-4-yl)-2,2-dimethylpropanoate (130 mg, 0.12 mmol), LiOH (29 mg, 1.22 mmol) dioxane (2.2 mL) and water (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 acetic acid (84 µl, 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 **Ex-77B**. 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* = 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).

EXAMPLE 78A

(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)acetic acid



(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)acetic acid was prepared using essentially the same procedures described in Example 77, using racemic **I-30** as starting material to form racemic 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.

Step A- 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. Into a flask was placed **I-A2** (1.0 g, 3.2 mmol), **I-30** (0.85 g, 3.6 mmol), potassium bicarbonate (390 mg, 3.9 mmol) and *t*-BuOH (100 mL). The resulting mixture was warmed at 70 °C for 8 h. reaction was cooled to RT and quenched by the addition of water. The resulting solution was extracted with EtOAc (3X) 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 chromatography using MeOH:DCM (1-10%) to afford the title compound.

Racemic methyl 2-(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)acetate was prepared as described in **Ex-77B** Step B and C using 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 as starting material.

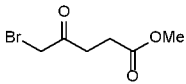
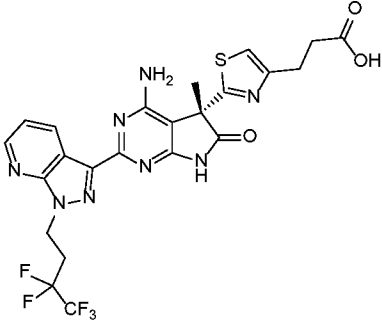
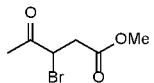
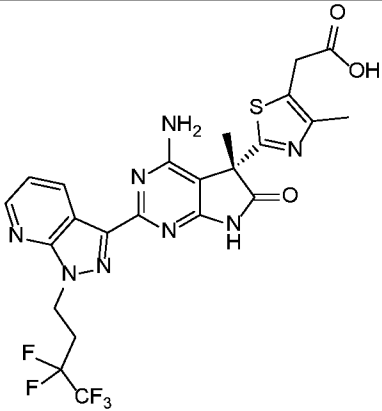
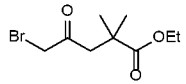
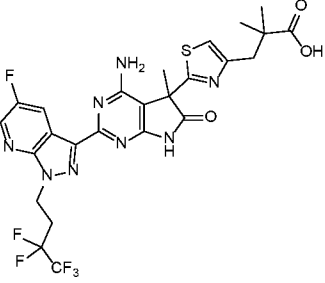
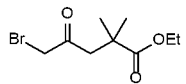
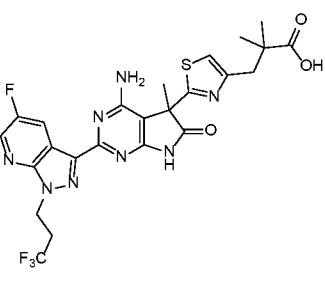
Step D. Racemic methyl 2-(2-{4-amino-5-methyl-6-oxo-2-(1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}thiazol-4-yl)acetate was resolved using Chiral SFC (CHIRALPAK[®] AD-H) to afford isomers **A** (faster eluting) and

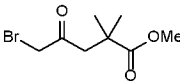
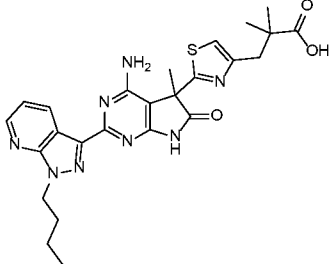
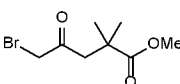
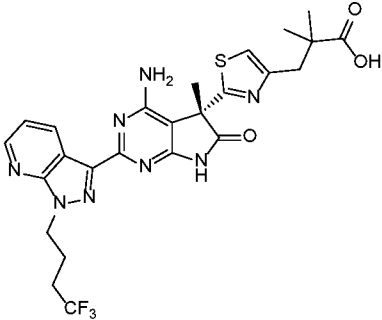
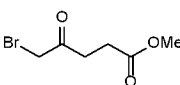
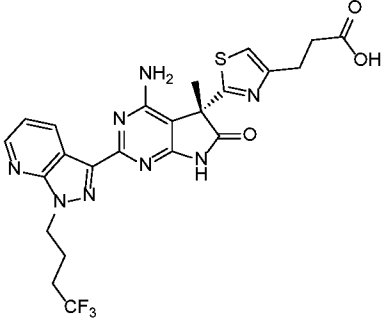
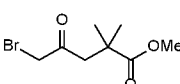
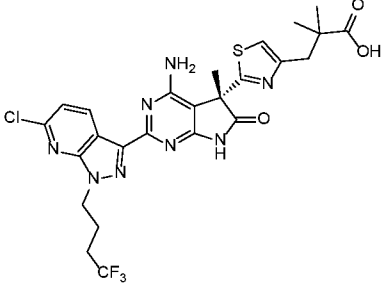
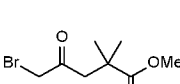
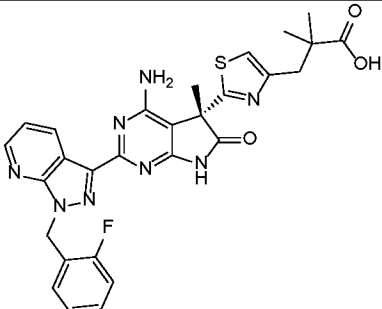
B (slower eluting). Isomer **A** was then hydrolysed using previously described conditions (step E in Ex-77B) to afford **Ex- 78A**. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.45 (br s, 1H), 11.43 (s, 1H), 9.04 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.64 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.45 (s, 1H), 7.38 (dd, *J* = 8.1, 4.5 Hz, 1H), 6.94 (br s, 2H), 4.88 (t, *J* = 6.6 Hz, 2H), 3.73 (s, 1H), 3.4-2.91 (m, 2H); 1.84 (s, 3H); *m/z* = 569 (M+1).

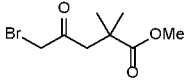
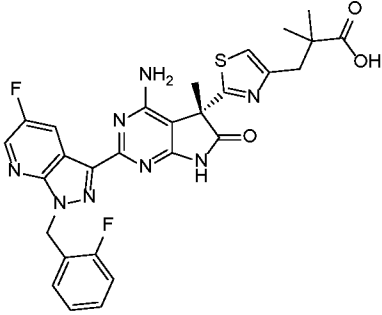
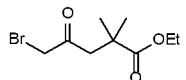
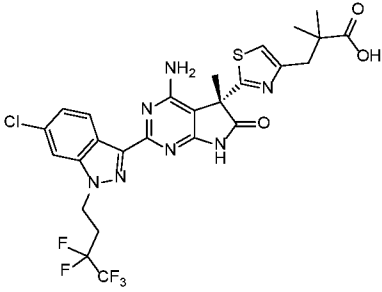
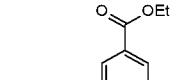
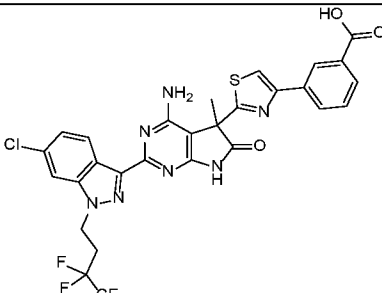
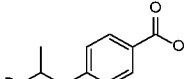
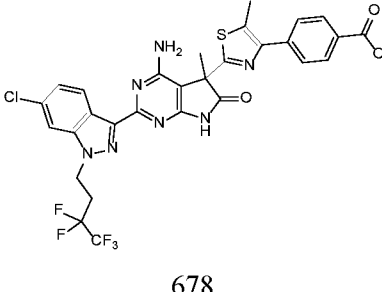
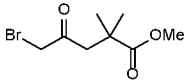
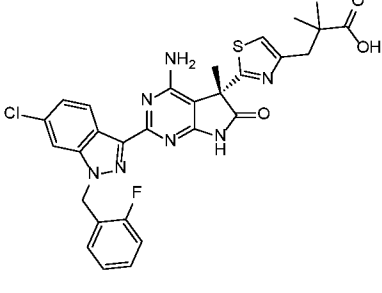
Using essentially the same procedures to those described in examples **77B** and **78A**, the following compounds in **Table 10** were prepared. The chirality of the compounds in **Table 15** results from the use of a chiral intermediate and/or the separation of isomers performed at Step D or E.

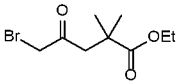
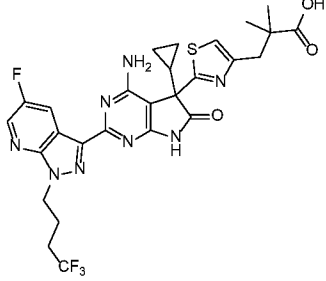
Table 15

Ex.	Int. SM / Chiral Resolution Step /Column	Step D Bromoketone	Structure / <i>m/z</i> (M+1)	Name
79B	I-40B/ Chiral Int.			(<i>S</i>)-3-(2-({4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-thiazol-4-yl)-3-methylbutanoic acid
80BA	I-40B/ Step D/ AD			(5 <i>S</i>)-2-(2-({4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-thiazol-4-yl)cyclopropanecarboxylic acid
81B	I-40B/ Chiral Int.			(<i>S</i>)-1-[(2-({4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-thiazol-4-yl)methyl)cyclopropane

			609	carboxylic acid
82B	I-40B/ Chiral Int.			(S)-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)propanoic acid
83B	I-40B/ Chiral Int.			(S)-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)-4-methyl-1,3-thiazol-5-yl)acetic acid
84A	I-30/ Step E/ AD			3-(2-(4-amino-2-[5-fluoro-1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid
85A	I-30/ Step D/ IA			3-(2-(4-amino-2-[5-fluoro-1-(3,3,3-trifluoropropyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid

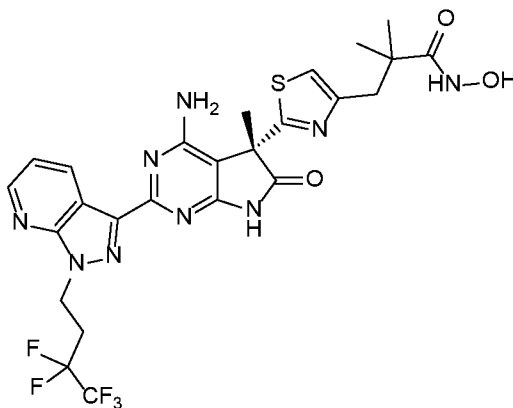
86A	I-30/ Step D/ IA		 521	3-{2-[4-amino-2-(1-butyl-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-thiazol-4-yl}-2,2-dimethylpropanoic acid
87B	I-40B/ Chiral Int.		 575	(S)-3-(2-{4-amino-5-methyl-6-oxo-2-[1-(4,4,4-trifluorobutyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid
88B	I-40B/ Chiral Int.		 547	(S)-3-(2-{4-amino-5-methyl-6-oxo-2-[1-(4,4,4-trifluorobutyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-thiazol-4-yl)propanoic acid
89B	I-40B/ Chiral Int.		 609	(S)-3-(2-{4-amino-2-[6-chloro-1-(4,4,4-trifluorobutyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid
90B	I-40B/ Chiral Int.		 573	(S)-3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid

91B	I-40B/ Chiral Int.			(S)-3-(2-((4-amino-2-((5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)-1,3-thiazol-4-yl)-2,2-dimethylpropanoyl)-2-methylpropanoic acid
92B	I-40B/ Chiral Int.			(S)-3-(2-((4-amino-2-((6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)-1,3-thiazol-4-yl)-2,2-dimethylpropanoyl)-2-methylpropanoic acid
93A	I-30/ Step D/ IA			3-(2-((4-amino-2-((6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)-1,3-thiazol-4-yl)benzoic acid
94B	I-30/ Step D/ AS			4-(2-((4-amino-2-((6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)-5-methyl-1,3-thiazol-4-yl)benzoic acid
95B	I-40B/ Chiral Int.			(S)-3-(2-((4-amino-2-((6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)-1,3-thiazol-4-yl)-2,2-dimethylpropanoyl)-2-methylpropanoic acid

96B	I-41B/ Chiral Int.		 619	3-(2-{4-amino-5-cyclopropyl-2-[5-fluoro-1-(4,4,4-trifluorobutyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}thiazol-4-yl)-2,2-dimethylpropanoic acid
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EXAMPLE 97B

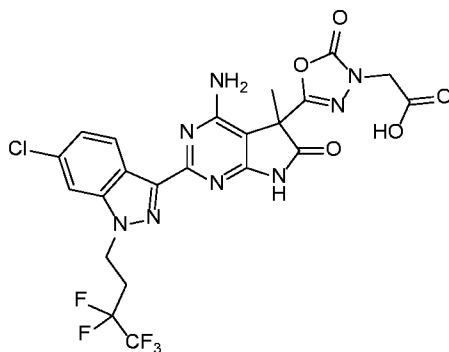
(S)-3-(2-{4-Amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-thiazol-4-yl)-N-hydroxy-2,2-dimethylpropanamide



A flask containing example **77B** (80 mg, 0.13 mmol), triethylamine (53 mg, 0.52 mmol), 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (100 mg, 0.26 mmol) in DMF (5 mL) was stirred for 10 min at RT before hydroxylammonium chloride (18 mg, 0.26 mmol) was added. The resulting mixture was stirred for 1 h at RT then was concentrated *in vacuo* to dryness. The residue was purified by silica gel column chromatography with MeOH: DCM (2-4%) then by reverse phase HPLC (ACN/water with 0.05% NH₄HCO₃ modifier) to afford the title compound **Ex-97B**. ¹H NMR (300 MHz, CD₃OD) δ 9.00 (dd, *J* = 1.5, 8.1 Hz, 1H), 8.58 (dd, *J* = 1.5, 4.5 Hz, 1H), 7.32 (dd, *J* = 4.5, 8.1 Hz, 1H), 7.12 (s, 1H), 4.91 (t, *J* = 7.2 Hz, 2H), 3.11-2.82 (m, 4H), 1.83 (s, 3H), 1.18 (s, 3H), 1.14 (s, 3H); *m/z* = 626 (*M* + 1).

EXAMPLE 98A

[5-{4-Amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-oxo-1,3,4-oxadiazol-3(2H)-yl]acetic acid



Step A - ethyl 4-amino-2-(6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl)-5-

methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine-5-carboxylate was prepared using

conditions similar to the those described for the synthesis of 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, using **I-A1** and **I-30** as starting material.

Step B- 4-amino-2-(6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl)-5-methyl-6-

oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine-5-carbohydrazide. A flask containing ethyl 4-

amino-2-(6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine-5-carboxylate (900 mg, 1.69 mmol) and hydrazine hydrate (863 mg, 16.89 mmol) in MeOH (10 mL) was stirred for 2 h at 70 °C. The solid was collected by filtration to afford the title compound which was used in Step C without purification.

Step C- 5-(4-amino-2-(6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl)-5-methyl-6-

oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)-1,3,4-oxadiazol-2(3H)-one. A flask containing 4-amino-2-(6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine-5-carbohydrazide (400 mg, 0.77 mmol) and *N,N*-carbonyldiimidazole (375 mg, 2.31 mmol) in DCM (25 mL) was stirred for 2 h at RT. The resulting mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with MeOH:DCM (2-4%) to afford the title compound.

Step D- ethyl 2-(5-(4-amino-2-(6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl)-5-

methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-oxo-1,3,4-oxadiazol-3(2H)-

yl)acetate. To a flask containing 5-(4-amino-2-(6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)-1,3,4-oxadiazol-2(3H)-one (150 mg, 0.28 mmol), and potassium carbonate (19 mg, 0.14 mmol) in DMF (20 mL) at -20 °C was added ethyl 2-bromoacetate (41.5 mg, 0.25 mmol) and the mixture was stirred for 5 h at -20 °C. The reaction was concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using MeOH:DCM (2-10%) to afford the title racemic product. The

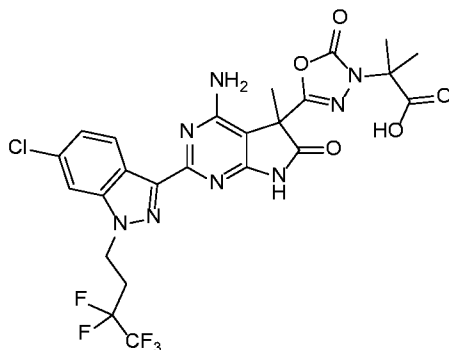
racemic material was resolved using chiral SFC (CHIRALCEL[®] OD-H column) to afford isomer **A** (faster eluting) and isomer **B** (slower eluting).

Step E- [5-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-oxo-1,3,4-oxadiazol-3(2H)-yl]acetic acid.

To a flask containing ethyl 2-(5-(4-amino-2-(6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-oxo-1,3,4-oxadiazol-3(2H)-yl)acetate isomer **A** (25 mg, 0.04 mmol), in THF (3 mL) was added LiOH (2.9 mg, 0.12 mmol) in water (1 mL). The resulting mixture was stirred for 2 h at RT before being concentrated *in vacuo*. The residue was diluted with hydrochloric acid (0.1 N, 1.1 mL), the solid was collected by filtration, washed with water and dried under vacuum to afford the title product **Ex-98A**. ¹H NMR (300 MHz, CD₃OD) δ 8.64 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 1.2 Hz, 1H), 7.24 (dd, *J* = 1.8, 8.7 Hz, 1H), 4.80-4.74 (m, 2H), 4.27 (s, 2H), 3.06-2.83 (m, 2H), 1.82 (s, 3H); *m/z* = 603 (*M* + 1).

EXAMPLE 99B

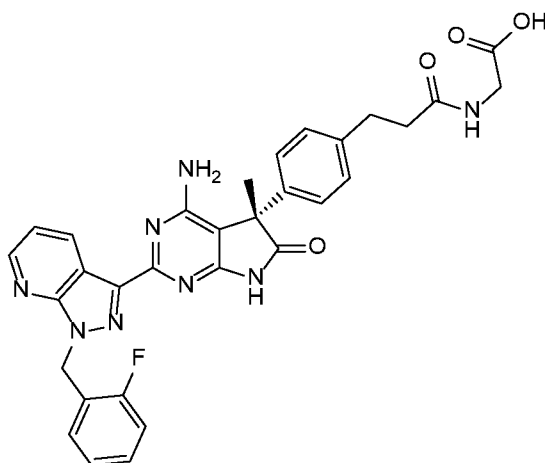
2-[5-{4-Amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-oxo-1,3,4-oxadiazol-3(2H)-yl]-2-methylpropanoic acid



The title compound was prepared using essentially the same procedures described in Example **98A**, using methyl 2-bromo-2-methylpropanoate as starting material. The racemic **Ex-99** was resolved using chiral SFC (Kromasil (R,R) WHELK-01 5/100 column) to afford isomers **Ex-99A** (faster eluting) and **Ex-99B** (slower eluting) of the title compound ¹H NMR (300 MHz, CD₃OD) δ 8.68 (d, *J* = 8.7 Hz, 1H), 7.78 (d, *J* = 1.5 Hz, 1H), 7.29 (dd, *J* = 1.5, 8.7 Hz, 1H), 4.95-4.80 (m, 2H), 3.11-2.86 (m, 2H), 1.86 (s, 3H), 1.75 (s, 3H), 1.74 (s, 3H); *m/z* = 631 (*M* + 1).

EXAMPLE 100B

(S)-(3-(4-{4-Amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoyl)glycine



Step A- (S)-tert-butyl (3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoyl)glycinate.

In a flask containing **Ex-21B** (20 mg, 0.037 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (12.19 mg, 0.04 mmol) in DMF (300 μ l) at RT was added triethylamine (52 μ l, 0.37 mmol). Then glycine *tert*-butyl ester hydrochloride (18 mg, 0.112 mmol) was added. The resulting mixture was stirred 20 min at RT. Volatiles were removed *in vacuo*, and then water was added and the solid was collected and dried under vacuum. The crude material was used directly in the next step.

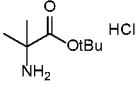
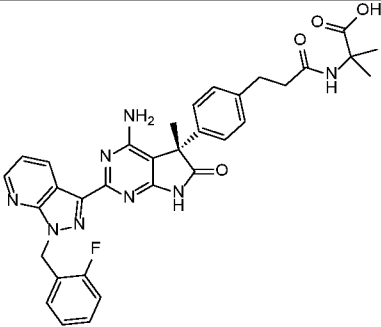
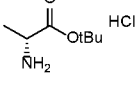
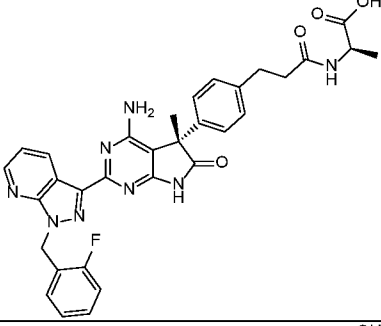
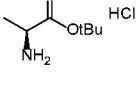
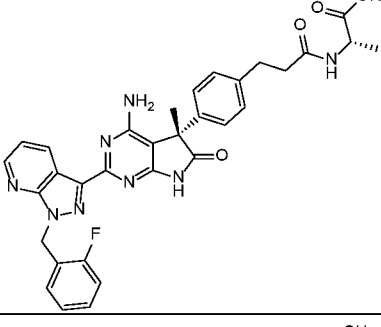
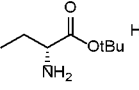
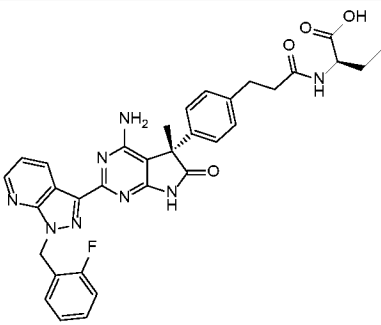
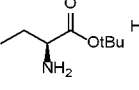
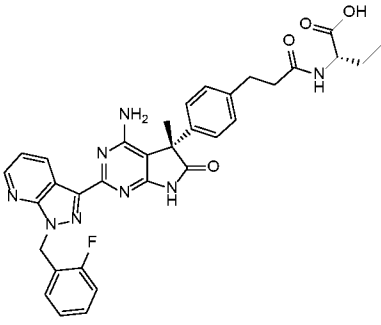
Step B- (S)-(3-(4-(4-amino-2-(1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)phenyl)propanoyl)glycine. To the crude product from step A was added trifluoroacetic acid (250 μ l, 3.24 mmol) and DCM (0.7 mL) and the reaction was stirred for 2 h at RT. The reaction mixture was then concentrated *in vacuo* to dryness. The mixture was filtered and purified by mass triggered reverse phase HPLC

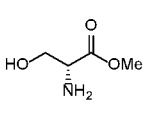
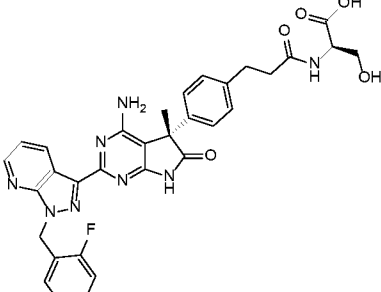
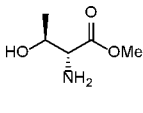
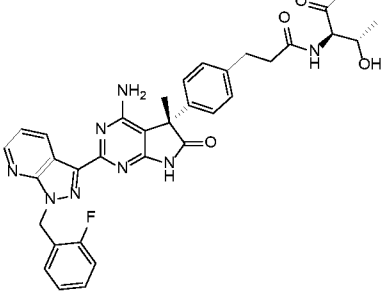
(ACN/water with 0.1% TFA modifier) to afford the title compound **Ex-100B** as the TFA salt. ^1H NMR (500 MHz, DMSO- d_6) δ 9.06 (dd, J = 8.0, 1.7 Hz, 1H), 8.65 (dd, J = 4.5, 1.7 Hz, 1H), 8.15 (d, J = 5.9 Hz, 1H), 7.43 – 7.31 (m, 2H), 7.23 – 7.10 (m, 7H), 6.55 (s, 2H), 5.83 (s, 2H), 3.71 (d, J = 5.8 Hz, 2H), 2.79 (t, J = 7.9 Hz, 2H), 2.41 (t, J = 8.0 Hz, 2H), 1.77 (s, 3H); m/z = 595.3 (M+1).

Using a similar procedure to that described in **Ex-100B**, the following compounds in **Table 16** were prepared using from commercial starting reagents or compounds known in the literature.

Methyl esters were hydrolysed using lithium hydroxide conditions previously described.

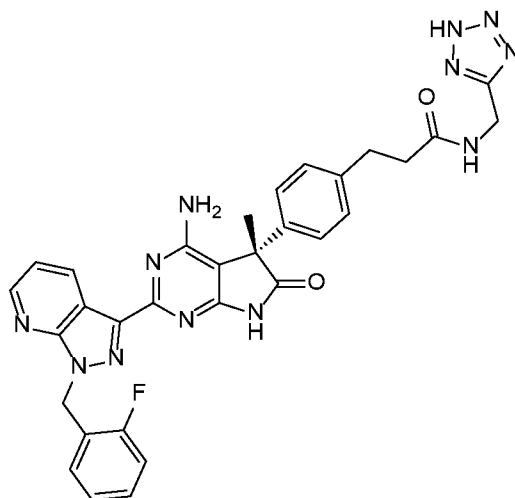
Table 16

Ex.	Step A amine	Structure	Name	<i>m/z</i> (M+1)
101B			(<i>S</i>)-2-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanamido)-2-methylpropanoic acid	623
102B			(5 <i>S</i>)-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoyl)-D-alanine	609
103B			(5 <i>S</i>)-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoyl)-L-alanine	609
104B			(5 <i>S</i> ,2 <i>R</i>)-2-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanamido)butanoic acid	623
105B			(5 <i>S</i> ,2 <i>S</i>)-2-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanamido)butanoic acid	623

106B			(5 <i>S</i>)-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoyl)-D-serine	625
107B			(5 <i>S</i>)-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoyl)-D-threonine	639

EXAMPLE 108B

(*S*)-*N*-((2*H*-Tetrazol-5-yl)methyl)-3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamide

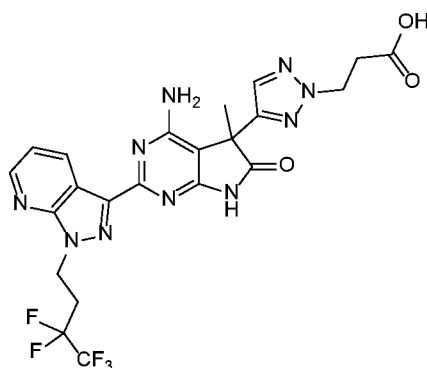


In a flask containing **Ex-21B** (20 mg, 0.037 mmol) and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (29.9 mg, 0.093 mmol) in DMF (300 μ l) at RT was added triethylamine (26 μ l, 0.186 mmol). Then (2-trityl-2*H*-tetrazol-5-yl)methanamine (40 mg, 0.11 mmol) was added. The resulting mixture was stirred 20 min at RT. The reaction was concentrated *in vacuo* to dryness then water was added and the solid was collected and dried under vacuum. The residue was treated with HCl (1 mL, 4 M in dioxane) and the resulting mixture was stirred at 80 $^{\circ}$ C then concentrated *in vacuo* to dryness and the residue was purified

by mass triggered reverse phase HPLC (ACN/water with 0.1% TFA modifier) to afford the title compound **Ex-108B** as the TFA salt. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.10 (s, 1H), 9.06 (dd, J = 8.1, 1.6 Hz, 1H), 8.65 (dd, J = 4.5, 1.6 Hz, 1H), 8.58 (t, J = 5.7 Hz, 1H), 7.43 – 7.32 (m, 2H), 7.29 – 7.11 (m, 7H), 6.55 (s, 2H), 5.84 (s, 2H), 4.53 (d, J = 5.6 Hz, 2H), 2.81 (t, J = 8.0 Hz, 2H), 2.44 (t, J = 8.0 Hz, 2H), 1.78 (s, 3H); m/z = 619 (M+1).

EXAMPLE 109B

3-(4-{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}-2H-1,2,3-triazol-2-yl)propanoic acid



Step A- 4-amino-5-ethynyl-5-methyl-2-(1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one. To a flask containing **I-A2** (400 mg, 1.30 mmol) and **I-10B** (272 mg, 1.43 mmol) in *t*-BuOH (10 mL) was added potassium bicarbonate (130 mg, 1.30 mmol). The resulting mixture was stirred at 70 °C for 16 h then quenched by the addition of brine and extracted with EtOAc (3X). The combined organic layer was washed with brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo*, the residue was purified by silica gel column chromatography with MeOH:DCM to afford the title compound.

Step B- 4-amino-5-methyl-2-(1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-(1H-1,2,3-triazol-4-yl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one. To a microwave vial containing 4-amino-5-ethynyl-5-methyl-2-(1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one (500 mg, 1.11 mmol) and bromotris(triphenylphosphine)copper (I) (103 mg, 0.11 mmol) in DMSO (22 mL) was added azidotrimethylsilane (770 μL , 5.54 mmol). The reaction mixture was microwaved at 120 °C for 1 h. The resulting mixture was cooled to RT and diluted with EtOAc and brine. To the organic phase was added aq. ammonium hydroxide solution and the resulting mixture was stirred 16 h. The aqueous was extracted with EtOAc (3X) dried over anhydr. MgSO_4 , filtered and the filtrate

was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with (EtOAc:EtOH 3:1): hexane gradient to afford the title compound.

Step C- Ethyl 3-(4-(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)-2H-1,2,3-triazol-2-yl)propanoate.

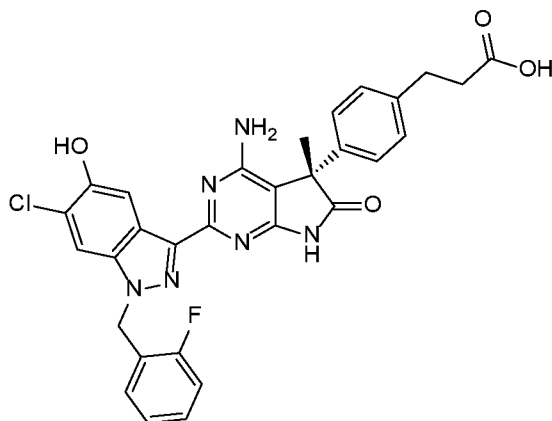
To a flask containing 4-amino-5-methyl-2-(1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-5-(1H-1,2,3-triazol-4-yl)-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one (160 mg, 0.29 mmol) and K₂CO₃ (121 mg, 0.87 mmol) in DMF (2.9 mL) was added ethyl acrylate (38 µl, 0.35 mmol). The resulting mixture was stirred 2 h at RT then diluted with EtOAc and brine. The organic layer was washed with brine, dried over anhydr. MgSO₄, and filtered. The filtrate was concentrated *in vacuo* and the residue was first purified by silica gel column chromatography with (EtOAc:EtOH 3:1):hexane then by mass triggered reverse phase HPLC (ACN/water with 0.1% TFA modifier) to afford the title compound as the TFA salt.

Step D- 3-(4-{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}-2H-1,2,3-triazol-2-yl)propanoic acid.

To a flask containing ethyl 3-(4-(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)-2H-1,2,3-triazol-2-yl)propanoate (22 mg, 0.037 mmol) in MeCN (1.8 mL) and water (1.8 mL) was added LiOH (5 mg, 0.18 mmol). The resulting mixture was stirred 30 min at RT then diluted in EtOAc and acetic acid (13 µl, 0.22 mmol). 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* and purified by silica gel column chromatography with (EtOAc:EtOH 3:1): Hexane to afford the title compound **Ex-109B**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.24 (s, 1H), 9.02 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.63 (dd, *J* = 4.5, 1.6 Hz, 1H), 7.73 (s, 1H), 7.37 (dd, *J* = 8.1, 4.5 Hz, 1H), 6.62 (s, 2H), 4.87 (t, *J* = 6.7 Hz, 2H), 4.49 (t, *J* = 7.2 Hz, 2H), 2.94 (dt, *J* = 19.1, 6.8 Hz, 3H), 2.71 (t, *J* = 7.1 Hz, 2H), 1.75 (s, 3H). *m/z* = 567.1 (M+1).

EXAMPLE 110B

(S)-3-(4-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-5-hydroxy-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid



Step A- (*S*)-methyl 3-(4-(4-amino-2-(6-chloro-1-(2-fluorobenzyl)-5-methoxy-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)phenyl)propanoate. A

5 flask containing **I-A24** (100 mg, 0.30 mmol), **I-11B** (99 mg, 0.30 mmol) and potassium bicarbonate (90 mg, 0.90 mmol) in *t*-BuOH (10 mL) was stirred for 16 h at 70 °C. The reaction mixture was concentrated *in vacuo* to dryness. The residue was purified by silica gel column chromatography with MeOH: DCM (0-5%) to afford the title compound.

Step B- (*S*)-3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-5-hydroxy-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid.

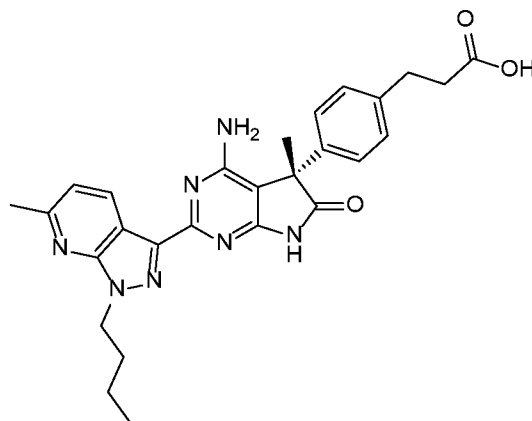
10 To a flask containing (*S*)-methyl 3-(4-(4-amino-2-(6-chloro-1-(2-fluorobenzyl)-5-methoxy-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)phenyl)propanoate (105 mg, 0.17 mmol) in DCM (10 mL) at 0 °C was added dropwise tribromoborane (1.0 mL, 10.6 mmol). The resulting mixture was stirred for 16 h at RT. The reaction was quenched by

15 the addition of ice water and the pH value of the mixture was adjusted to pH 7-8 by the addition of NaHCO₃. The resulting solution was extracted with EtOAc (3X), the organic layer was washed with brine, dried over anhydr. Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography with MeOH : DCM (1-6%) to afford the title compound **Ex-110B**, ¹H NMR (300 MHz, CD₃OD): δ 8.10 (s, 1H), 7.59 (s, 1H), 7.30-7.20 (m, 5H), 7.15-7.06 (m, 3H), 5.70 (s, 2H), 2.87 (t, *J* = 7.2 Hz, 2H), 2.56 (t, *J* = 7.2 Hz, 2H), 1.84 (s, 3H); *m/z* = 587 (*M* + 1).

20

EXAMPLE 111B

(*S*)-3-{4-[4-amino-2-(1-butyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid



Step A- (S)-methyl 3-(4-(4-amino-2-(1-butyl-6-chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)phenyl)propanoate. A flask containing **I-A36** (50 mg, 0.20 mmol), **I-11B** (65 mg, 0.20 mmol) and potassium bicarbonate (60 mg, 0.60 mmol) in *t*-BuOH (5 mL) was stirred for 16 h at 75 °C. The reaction was cooled to RT and quenched by the addition of water. The resulting solution was extracted with DCM (3X), 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 chromatography using MeOH: DCM (0-3%) to afford the title product.

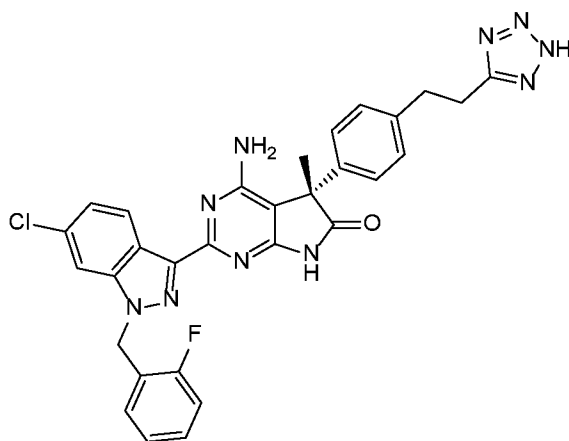
Step B- (S)-methyl 3-(4-(4-amino-2-(1-butyl-6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)phenyl)propanoate. In a flask under inert atmosphere of nitrogen were placed (S)-methyl 3-(4-(4-amino-2-(1-butyl-6-chloro-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)phenyl)propanoate (140 mg, 0.26 mmol), bis(triphenylphosphine)palladium(II) chloride (28 mg, 0.039 mmol) and THF (10 mL). The resulting mixture was stirred for 30 min before dimethylzinc (1.57 mL, 1.57 mmol, 1 M in THF) was added. The mixture was stirred for 16 h at RT. The reaction was quenched by the addition of aq. sat. NH₄Cl, extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo* and the residue was first purified by silica gel column chromatography with MeOH:DCM (0-10%) then by reverse phase HPLC (ACN/water with 0.05% NH₄HCO₃ modifier) to afford the title compound.

Step C- (S)-3-{4-[4-amino-2-(1-butyl-6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl]phenyl}propanoic acid. To a flask containing (S)-methyl 3-(4-(4-amino-2-(1-butyl-6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)phenyl)propanoate (70 mg, 0.14 mmol) in THF (8 mL) was added LiOH (16 mg, 0.68 mmol) in water (0.5 mL). The resulting

mixture was stirred for 16 h at RT before been concentrated *in vacuo*. The residue was diluted with water (2 mL) and hydrochloric acid (6.8 mL, 0.1 N) was added. The solid was collected by filtration and dried under vacuum to afford the title product **Ex-111B**. ¹H NMR (400 MHz, CD₃OD) δ 8.88 (d, *J* = 8.0 Hz, 1H), 7.30-7.20 (m, 5H), 4.59 (t, *J* = 6.8 Hz, 2H), 2.90 (t, *J* = 7.6 Hz, 2H), 2.69 (s, 3H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.02-1.95 (m, 2H), 1.87 (s, 3H), 1.40-1.34 (m, 2H), 0.97 (t, *J* = 7.6 Hz, 3H); *m/z* = 500 (M + 1).

EXAMPLE 112B

(S)-4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5-{4-[2-(2*H*-tetrazol-5-yl)ethyl]phenyl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one



Step A- (S)-3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methynyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamide. To a flask containing **Ex-47B** (1.0 g, 1.58 mmol) in DMF (10 mL) was added *N,N'*-carbonyldiimidazole (1.28 g, 7.88 mmol). The mixture was stirred for 30 min at RT and NH₄Cl (0.17 g, 3.15 mmol) was added. The resulting mixture was stirred for 16 h at RT then poured into water and extracted with EtOAc (3 X). 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 chromatography using MeOH:DCM (0-5%) to afford the title compound.

Step B- (S)-3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanenitrile. To a flask containing (S)-3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamide (800 mg, 1.40 mmol) and pyridine (0.5 mL, 6.18 mmol) in DCM (5 mL) at 0 °C was added dropwise 2,2,2-trifluoroacetic anhydride (0.5 mL, 3.54 mmol). The mixture was stirred for 1 h at RT. The reaction was then diluted with MeOH (20 mL) and concentrated *in vacuo*. The residue was diluted with water,

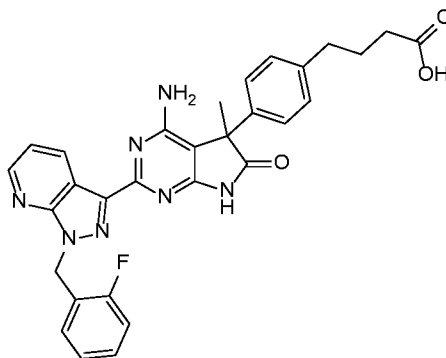
extracted with EtOAc (3X) and the organic layers were combined, dried over anhydr. Na_2SO_4 , filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using MeOH:DCM (0-5%) to afford the title product.

Step C- (S)-4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5-{4-[2-(2H-

tetrazol-5-yl)ethyl]phenyl}-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one. To a flask containing (S)-3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanenitrile (170 mg, 0.31 mmol) and dibutylstannanone (15.3 mg, 0.062 mmol) in toluene (10 mL) was added azidotrimethylsilane (177 mg, 1.54 mmol). The mixture was stirred for 16 h at 100 °C then the mixture was concentrated *in vacuo*. The residue was first purified by silica gel column chromatography with MeOH:DCM (0-5%) then by reverse phase HPLC (ACN/water with 0.05% NH_4HCO_3 modifier) to afford the title compound **Ex-112B**. ^1H NMR (300 MHz, CD_3OD) δ 8.66 (d, J = 8.7 Hz, 1H), 7.63 (s, 1H), 7.35-7.05 (m, 9H), 5.76 (s, 2H), 3.16-2.96 (m, 4H), 1.83 (s, 3H); m/z = 595 ($M + 1$).

EXAMPLE 113A

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



Step A- 4-Amino-5-(4-bromophenyl)-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one. A flask containing **I-A16** (250 mg, 0.82 mmol), **I-21A** (263 mg, 0.82 mmol) and potassium bicarbonate (180 mg, 1.80 mmol) in *t*-BuOH (10 mL) was stirred at 70 °C for 16 h. The reaction mixture was concentrated *in vacuo* to dryness. The residue was purified by silica gel column chromatography with MeOH:DCM (0-10%) to afford the title compound. m/z = 546 ($M+1$).

Step B- ethyl 4-(4-{4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)butanoate. To a flask under a inert atmosphere of nitrogen, containing 4-amino-5-(4-bromophenyl)-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-

d]pyrimidin-6-one (150 mg, 0.28 mmol) and second generation Xphos precatalyst (43 mg, 0.055 mmol) in THF (0.5 mL) was added 4-ethoxy-4-oxobutylzinc bromide (3.3 mL, 1.65 mmol). The resulting mixture was stirred at 55 °C for 16 h. The reaction was quenched by the addition of aq. sat. NH₄Cl, extracted with EtOAc (3X). The organic layers were combined, dried over anhydr.

Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with MeOH:DCM (0-10%) to afford the title compound.

Step C - 4-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)butanoic acid. To a flask

containing ethyl 4-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-

methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)butanoate (100 mg, 0.17

mmol) in THF (4 mL) was added LiOH (72 mg, 1.72 mmol) in water (4 mL). The resulting

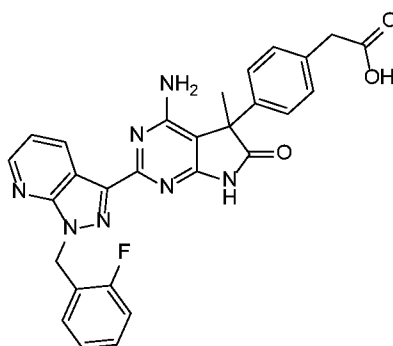
mixture was stirred for 16 h at RT before being concentrated *in vacuo*. The residue was diluted

with hydrochloric acid (0.1 N, 17.2 mL), the solid was collected by filtration, washed with water and dried under vacuum to afford the title product **Ex-113A**. ¹H NMR (300 MHz, CD₃OD): δ

9.10 (d, *J* = 8.1 Hz, 1H), 8.61 (dd, *J* = 4.5 Hz, 1.2 Hz, 1H), 7.40-7.06 (m, 9H), 5.92 (s, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.28 (t, *J* = 7.2 Hz, 2H), 1.98-1.85 (m, 5H); *m/z* = 552 (*M* + 1).

EXAMPLE 114A

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



Step A- *tert*-butyl 2-(4-(4-amino-2-{1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)acetate. In a microwave vial were placed 4-amino-5-(4-bromophenyl)-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-

3-yl]-5-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one (**Ex-113A**, step A, isomer **A**)

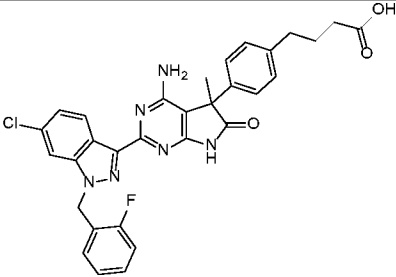
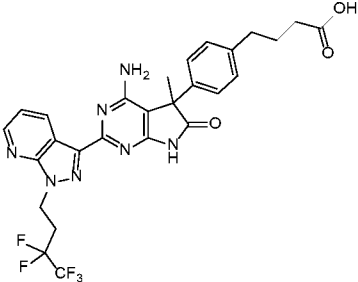
(150 mg, 0.28 mmol), bis(dibenzylideneacetone)palladium (32 mg, 0.055 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (32 mg, 0.11 mmol) and (2-(*tert*-butoxy)-2-oxoethyl)zinc(II) bromide (1.07 g, 4.13 mmol) in THF(15 mL). The reaction mixture was stirred for 1 h at RT and

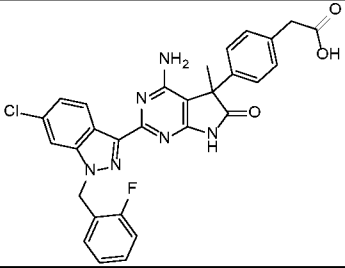
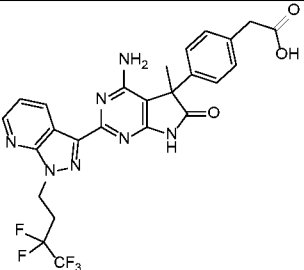
then microwaved for 1 h at 120 °C. The reaction was quenched by the addition of aq. sat. NH₄Cl, extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by reverse phase HPLC (ACN/water with 0.05% NH₄HCO₃ modifier) to afford the title compound.

- 5 **Step B- (4-{4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)acetic acid.** Into a flask were placed *tert*-butyl 2-(4-(4-amino-2-{1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl}-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)phenyl)acetate (65 mg, 0.11 mmol), DCM (5 mL) and trifluoroacetic acid (1 mL). The resulting mixture was stirred for 16 h at RT. The
- 10 reaction was concentrated *in vacuo* then diluted with water. The pH value was adjusted to pH 10 by addition of sodium hydroxide (1 N) and then, the pH value was adjusted to pH 6 with hydrochloric acid (1 N), the solid was collected by filtration, washed with water and dried under vacuum to afford the title product **Ex-114A**. ¹H NMR (300 MHz, CD₃OD) δ 9.04 (dd, *J* = 1.8 Hz, 8.4 Hz, 1H), 8.60 (dd, *J* = 1.8 Hz, 4.5 Hz, 1H), 7.39-7.24 (m, 6H), 7.13-7.01 (m, 3H), 5.90 (s,
- 15 2H), 3.57 (s, 2H), 1.86 (s, 3H); *m/z* = 524 (*M* + 1).

Using essentially the same procedure described in examples 113A and 114A, the following compounds in **Table 17** were prepared.

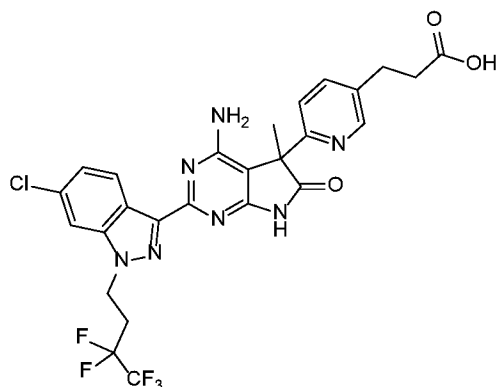
Table 17

Ex	Structure	Name	<i>m/z</i> (<i>M</i> +1)
115A		4-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)butanoic acid	585
116A		4-(4-{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}phenyl)butanoic acid	590

117A		2-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)acetic acid	557
118A		2-(4-{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}phenyl)acetic acid	562

EXAMPLE 119B

3-(6-{4-Amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}pyridin-3-yl)propanoic acid



5

Step A- 4-amino-5-(5-bromopyridin-2-yl)-2-(6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one. A flask containing **I-A1** (200 mg, 0.59 mmol), **I-19** (189 mg, 0.587 mmol) and potassium bicarbonate (88 mg, 0.88 mmol) in *t*-BuOH (10 mL) was stirred for 16 h at 75 °C. The reaction mixture was concentrated *in vacuo* to dryness. The residue was purified by silica gel column chromatography with MeOH:DCM (0-10%) to afford the title compound.

10

Step B- methyl 3-(6-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}pyridin-3-yl)acrylate. In a flask under a inert atmosphere of nitrogen were placed 4-amino-5-(5-bromopyridin-2-yl)-2-(6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl)-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one (300 mg, 0.49 mmol), palladium (II) acetate (22 mg, 0.097 mmol), tri-*tert*-butylphosphine (394 mg, 0.20 mmol), triethylamine (0.14 mL, 0.97 mmol) and methyl acrylate

15

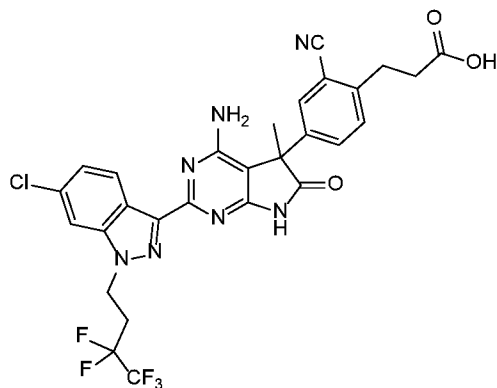
(126 mg, 1.46 mmol) in DMF (8 mL). The resulting mixture was stirred for 16 h at 100 °C. The reaction was cooled to RT and quenched by the addition of water. The resulting solution was extracted with EtOAc (3X) and the organic layers were combined, dried over anhydr. Na₂SO₄, filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using EtOAc: petroleum ether (20%-100%) to afford the title product.

Step B- methyl 3-(6-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-3-yl)propanoate. A flask containing methyl 3-(6-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-3-yl)acrylate (300 mg, 0.48 mmol), 4-methylbenzenesulfonhydrazide (269 mg, 1.45 mmol), sodium acetate trihydrate (328 mg, 2.41 mmol) in a mixture water (1 mL) and dimethoxyethane (10 mL) was stirred for 16 h at 80 °C. The reaction was cooled to RT and quenched by the addition of water. The resulting solution was extracted with EtOAc (3X) 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 chromatography using EtOAc: petroleum ether (30%-70%) then by reverse phase HPLC (ACN/water with 0.05% NH₄HCO₃ modifier) to afford the racemic title compound. The racemic material was resolved using chiral SFC (CHIRALPAK[®] IC column) to afford isomer **A** (faster eluting) and isomer **B** (slower eluting).

Step C- 3-(6-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-3-yl)propanoic acid. To a flask containing methyl 3-(6-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-3-yl)propanoate isomer **B** (70 mg, 0.11 mmol) in MeOH (2 mL) was added LiOH (13 mg, 0.56 mmol) in water (1 mL). The resulting mixture was stirred for 16 h at RT before been concentrated *in vacuo*. The residue was diluted with hydrochloric acid (0.1 N, 5.6 mL), the solid was collected by filtration, washed with water and dried under vacuum to afford the title product **Ex-119B**. ¹H NMR (300 MHz, CD₃OD) δ 8.64 (dd, *J* = 8.7, 3.3 Hz, 1H), 8.50 (d, *J* = 2.1 Hz, 1H), 7.73 (s, 1H), 7.70 (d, *J* = 2.4 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 4.79 (t, *J* = 6.6 Hz, 2H), 3.01-2.84 (m, 4H), 2.64 (t, *J* = 7.5 Hz, 2H), 1.89 (s, 3H); *m/z* = 610 (*M* + 1).

EXAMPLE 120B

3-(4-{4-Amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-cyanophenyl)propanoic acid



Step A- methyl 3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-bromophenyl)propanoate. A flask containing **I-A1** (550 mg, 1.61 mmol), **I-14** (657 mg, 1.61 mmol) and potassium

bicarbonate (485 mg, 4.84 mmol) in *t*-BuOH (25 mL) was stirred for 16 h at 70 °C. The reaction was cooled to RT and quenched by the addition of brine. The resulting solution was extracted with EtOAc (3X) 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 chromatography using MeOH:DCM (0-2%) to afford the title racemic product. The racemic material was resolved using chiral SFC (Kromasil (R,R)WHELK-01 5/100 column) to afford isomer **A** (faster eluting) and isomer **B** (slower eluting). *m/z* = 703 (M+1).

Step B- methyl 3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-cyanophenyl)propanoate. A flask under an inert atmosphere of nitrogen containing methyl 3-(4-{4-amino-2-[6-chloro-1-

(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-bromophenyl)propanoate isomer **B** (120 mg, 0.17 mmol), zinc cyanide (26 mg, 0.22 mmol), tris(dibenzylideneacetone)dipalladium-chloroform adduct (17.7 mg, 0.017 mmol), 1,1'-bis(diphenylphosphino)ferrocene (19 mg, 0.034 mmol) and zinc (11 mg, 0.17 mmol) in DMF (10 mL) was stirred for 1 h at 120 °C. The reaction was cooled to RT and quenched by the addition of brine. The resulting solution was extracted with EtOAc (3X) 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 chromatography using MeOH:DCM (0-2%) to afford the title product.

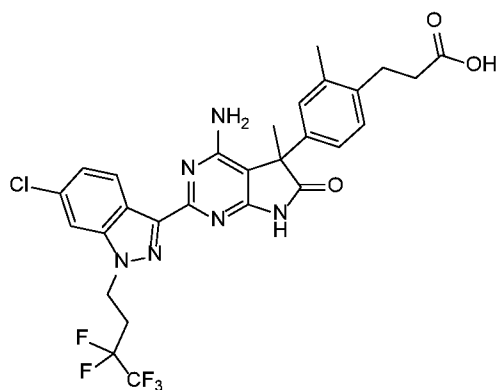
Step C- 3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-cyanophenyl)propanoic acid.

To a flask containing methyl 3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-

cyanophenyl)propanoate (58 mg, 0.090 mmol) in THF (2 mL) was added LiOH (38 mg, 0.90 mmol) in water (2 mL). The resulting mixture was stirred for 1 h at RT before been concentrated *in vacuo*. The residue was diluted with hydrochloric acid (0.1 N, 8.9 mL), the solid was collected by filtration, washed with water and dried under vacuum to afford the title product **Ex-120B**. ¹H NMR (300 MHz, CD₃OD) δ 8.64 (d, *J* = 8.7 Hz, 1H), 7.72 (s, 1H), 7.68 (s, 1H), 7.52-7.42 (m, 2H), 7.24 (d, *J* = 8.7 Hz, 1H), 4.82-4.76 (m, 2H), 3.10 (t, *J* = 7.2 Hz, 2H), 3.00-2.82 (m, 2H), 2.70-2.60 (m, 2H), 1.87 (s, 3H); *m/z* = 634 (*M* + 1).

EXAMPLE 121B

3-(4-{4-Amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-methylphenyl)propanoic acid



Step A- methyl 3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-methylphenyl)propanoate.

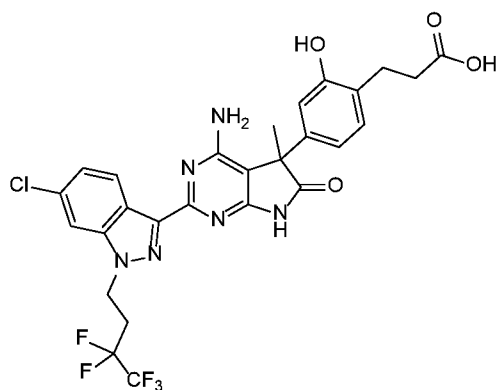
To a microwave tube under an inert atmosphere of nitrogen was added methyl 3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-bromophenyl)propanoate isomer **B** (100 mg, 0.14 mmol), 1,1'-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (9.3 mg, 0.014 mmol) potassium carbonate (197 mg, 1.43 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (322 mg, 1.28 mmol) and dioxane (10 mL). The tube was flushed with nitrogen for 4 min then microwaved for 2 h at 70 °C. The reaction was cooled to RT and quenched by the addition of brine. The resulting solution was extracted with EtOAc (3X) 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 chromatography using MeOH:DCM (0-2%) to afford the title product.

Step B- 3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-methylphenyl)propanoic acid. To a flask containing methyl 3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-methylphenyl)propanoate

(55 mg, 0.086 mmol) in THF (2 mL) was added LiOH (36 mg, 0.86 mmol) in water (2 mL). The resulting mixture was stirred for 1 h at RT before being concentrated *in vacuo*. The residue was diluted with hydrochloric acid (0.1 N, 8.6 mL), the solid was collected by filtration, washed with water and dried under vacuum to afford the title product **Ex-121B**. ¹H NMR (300 MHz, CD₃OD) δ 8.64 (d, *J* = 8.7 Hz, 1H), 7.72 (s, 1H), 7.24 (d, *J* = 8.7 Hz, 1H), 7.17-7.07 (m, 3H), 4.80-4.76 (m, 2H), 3.00-2.82 (m, 4H), 2.51 (t, *J* = 7.8 Hz, 2H), 2.29 (s, 3H), 1.87 (s, 3H); *m/z* = 623 (*M* + 1).

EXAMPLE 122B

3-(4-{4-Amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-hydroxyphenyl)propanoic acid



Step A- methyl 3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-methoxyphenyl)propanoate.

A flask containing **I-A1** (143 mg, 0.42 mmol), **I-17** (150 mg, 0.42 mmol) and potassium bicarbonate (51 mg, 0.51 mmol) in *t*-BuOH (5 mL) was stirred for 16 h at 70 °C. The reaction mixture was concentrated *in vacuo* to dryness. The residue was purified by silica gel column chromatography with MeOH:DCM (0-10%) to afford the racemic title compound. The racemic material was resolved using Chiral SFC (Phenomenex Lux 5u Cellulose-4) to afford isomer **A** (faster eluting) and isomer **B** (slower eluting).

Step B- 4-amino-2-(6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl)-5-methyl-5-(2-oxochroman-7-yl)-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one. To a flask containing

methyl 3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-methoxyphenyl)propanoate isomer **A** (60 mg, 0.092 mmol) in DCM (1 mL) at 0 °C was added dropwise tribromoborane (0.2 mL, 2.11 mmol). The resulting mixture was stirred 1 h at 0 °C then 16 h at RT. The reaction was then quenched by the addition of sodium hydroxide. The pH value of the solution was adjusted to pH

6 but the addition of hydrochloric acid (2 N). The resulting solution was extracted with EtOAc (3X) and the organic layers were combined, dried over anhydr. Na₂SO₄, filtered and the filtrate was concentrated *in vacuo* to dryness to afford the title product.

Step C- methyl 3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-hydroxyphenyl)propanoate.

A flask containing 4-amino-2-(6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl)-5-methyl-5-(2-oxochroman-7-yl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one (60 mg, 0.099 mmol) in MeOH (4 mL) was stirred for 3 h at 110 °C. The reaction mixture was concentrated *in vacuo* to dryness to afford the title product.

Step D- 3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-hydroxyphenyl)propanoic acid.

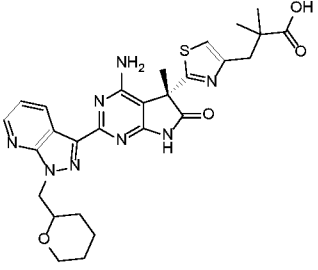
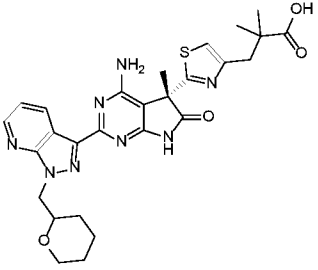
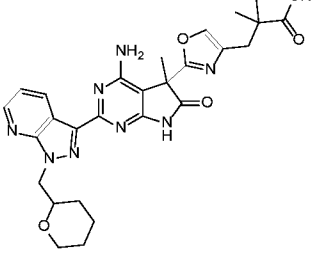
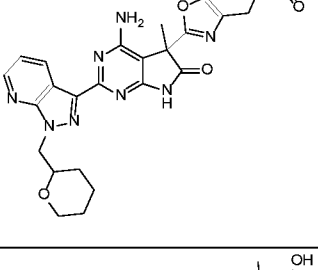
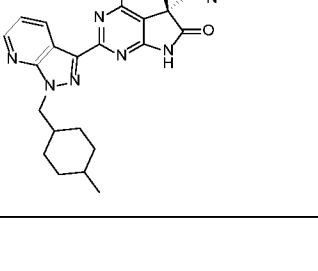
To a flask containing methyl 3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-2-hydroxyphenyl)propanoate (60 mg, 0.094 mmol) in THF (4 mL) was added sodium hydroxide (19 mg, 0.47 mmol) in water (0.5 mL). The resulting mixture was stirred for 6 h at RT then concentrated *in vacuo* to dryness. The residue was diluted with water and the pH was adjusted to pH 4 with hydrochloric acid (1 N). The resulting solution was extracted with EtOAc (3X) and the organic layers were combined, dried over anhydr. Na₂SO₄, filtered and the filtrate was concentrated *in vacuo* to dryness. The residue was diluted with EtOAc: DCM : hexane (1:1:4) and the solid was collected by filtration and dried under vacuum to afford the title product **Ex-122B**. ¹H NMR (400 MHz, CD₃OD): δ 8.70 (d, *J* = 8.8 Hz, 1H), 7.78 (s, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.14 (d, *J* = 2.4 Hz, 1H), 7.04 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 4.84 (t, *J* = 7.2 Hz, 2H), 3.03-2.86 (m, 4H), 2.60 (t, *J* = 7.6 Hz, 2H), 1.85 (s, 3H); *m/z* = 625 (M + 1).

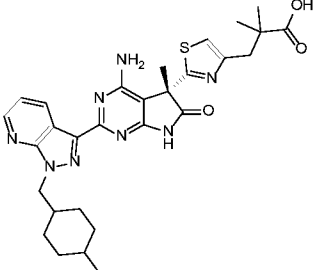
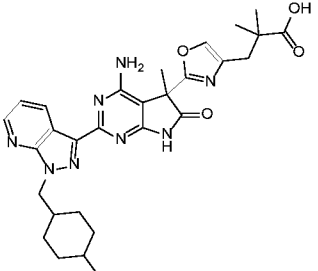
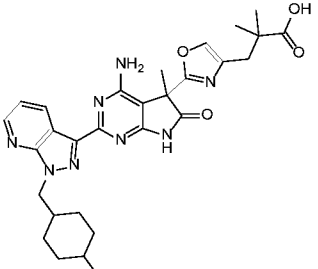
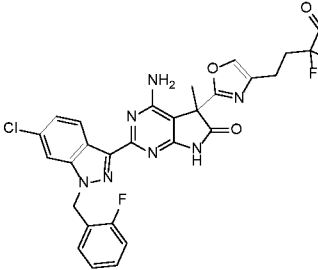
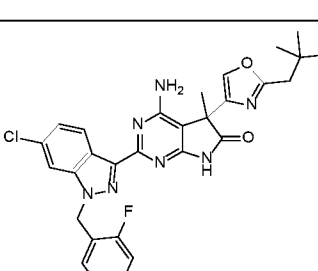
EXAMPLES 123A-139B

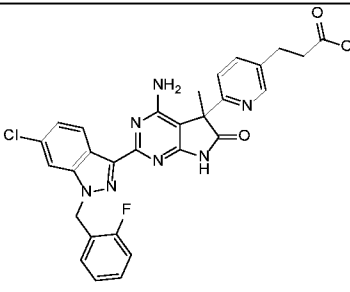
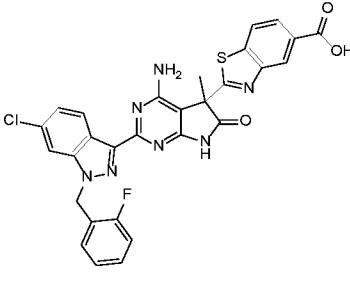
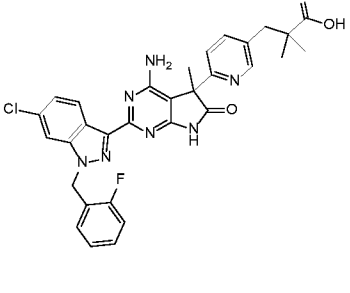
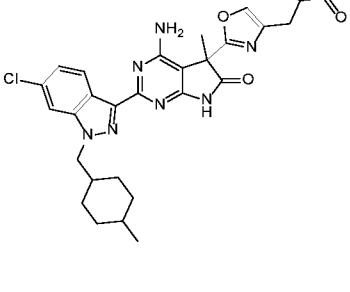
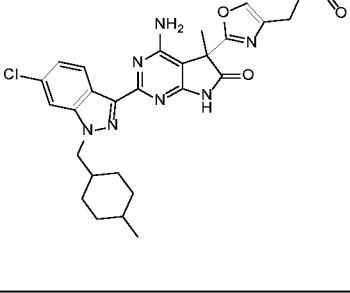
Using essentially the same procedure as described in **Ex-1A**, the following compounds in **Table 18** were prepared.

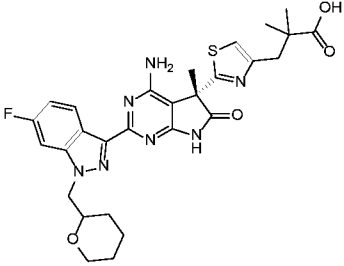
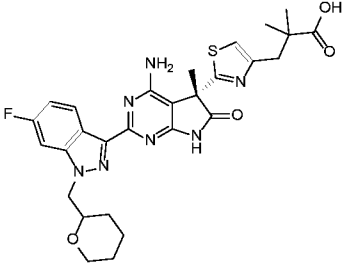
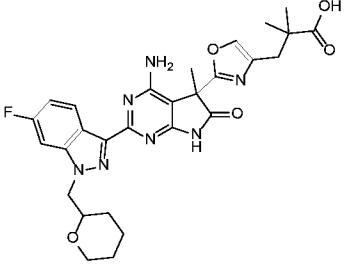
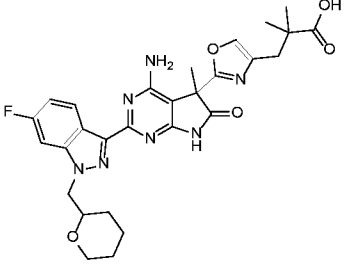
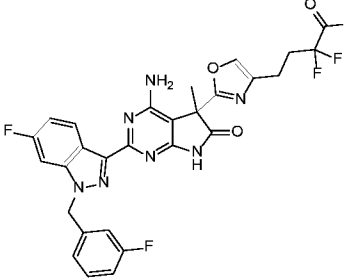
Table 18

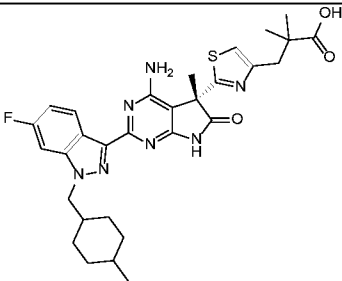
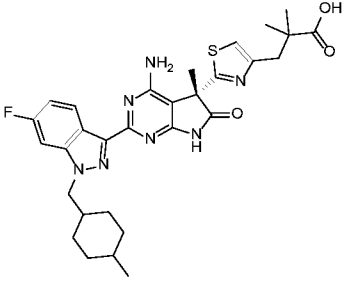
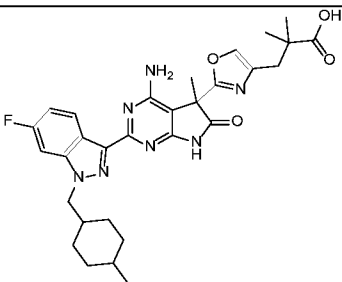
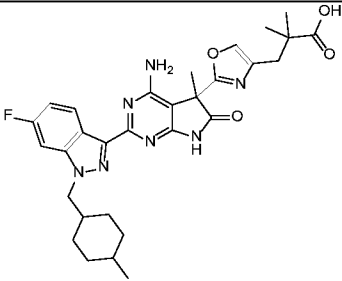
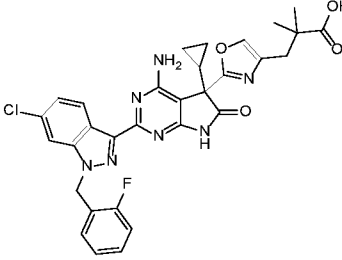
Ex.	Int. SM	Chiral Resolution Column	Structure	Name	<i>m/z</i> (M+1)
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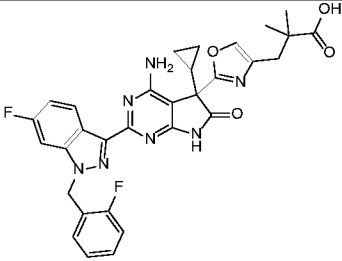
123AA	I-35A	Lux Cellulose-4		(5 <i>S</i>)-3-{2-[4-amino-5-methyl-6-oxo-2-{1-[tetrahydro-2 <i>H</i> -pyran-2-ylmethyl]-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl}-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-thiazol-4-yl}-2,2-dimethylpropanoic acid	563
123AB	I-35A	Lux Cellulose-4		(5 <i>S</i>)-3-{2-[4-amino-5-methyl-6-oxo-2-{1-[tetrahydro-2 <i>H</i> -pyran-2-ylmethyl]-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl}-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-thiazol-4-yl}-2,2-dimethylpropanoic acid	563
124AA	I-42A	IC		3-{2-[4-amino-5-methyl-6-oxo-2-{1-[tetrahydro-2 <i>H</i> -pyran-2-ylmethyl]-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl}-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid	547
124AB	I-42A	IC		3-{2-[4-amino-5-methyl-6-oxo-2-{1-[tetrahydro-2 <i>H</i> -pyran-2-ylmethyl]-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl}-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid	547
125AA	I-35A	AD-H		(5 <i>S</i>)-3-{2-[4-amino-5-methyl-2-{1-[4-methylcyclohexylmethyl]-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl}-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-thiazol-4-yl}-2,2-dimethylpropanoic acid	575

125AB	I-35A	AD-H		(5 <i>S</i>)-3-{2-[4-amino-5-methyl-2-{1-[4-methylcyclohexylmethyl]-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl}-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-thiazol-4-yl}-2,2-dimethylpropanoic acid	575
126AA	I-42A	AD		3-{2-[4-amino-5-methyl-2-{1-[4-methylcyclohexylmethyl]-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl}-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid	559
126AB	I-42A	AD		3-{2-[4-amino-5-methyl-2-{1-[4-methylcyclohexylmethyl]-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl}-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid	559
127A	I-54	IA		4-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-difluorobutanoic acid	612
128A	I-64	IA		3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-2-yl)-2,2-dimethylpropanoic acid	590

129A	I-62	Chiral Cellulose- SB		3-(6-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}pyridin-3-yl)propanoic acid	572
130A	I-67	ID		2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-benzothiazole-5-carboxylic acid	600
131B	I-20	IC		3-(6-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}pyridin-3-yl)-2,2-dimethylpropanoic acid	600
132AA	I-42A	Chiral Cellulose- SB		3-{2-[4-amino-2-{6-chloro-1-[4-methylcyclohexylmethyl]-1H-indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid	592
132AB	I-42A	Chiral Cellulose- SB		3-{2-[4-amino-2-{6-chloro-1-[4-methylcyclohexylmethyl]-1H-indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid	592

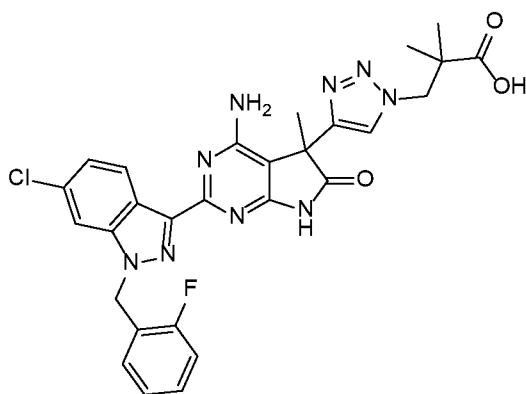
133AA	I-35A	IC		(5 <i>S</i>)-3-{2-[4-amino-2-{6-fluoro-1-[tetrahydro-2 <i>H</i> -pyran-2-ylmethyl]-1 <i>H</i> -indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-thiazol-4-yl}-2,2-dimethylpropanoic acid	580
133AB	I-35A	IC		(5 <i>S</i>)-3-{2-[4-amino-2-{6-fluoro-1-[tetrahydro-2 <i>H</i> -pyran-2-ylmethyl]-1 <i>H</i> -indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-thiazol-4-yl}-2,2-dimethylpropanoic acid	580
134AA	I-42A	IC		3-{2-[4-amino-2-{6-fluoro-1-[tetrahydro-2 <i>H</i> -pyran-2-ylmethyl]-1 <i>H</i> -indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid	564
134AB	I-42A	IC		3-{2-[4-amino-2-{6-fluoro-1-[tetrahydro-2 <i>H</i> -pyran-2-ylmethyl]-1 <i>H</i> -indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid	564
135A	I-54	IA		4-(2-{4-amino-2-[6-fluoro-1-(3-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-oxazol-4-yl)-2,2-difluorobutanoic acid	596

136AA	I-35A	AD-H		(5 <i>S</i>)-3-{2-[4-amino-2-{6-fluoro-1-[4-methylcyclohexylmethyl]-1 <i>H</i> -indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-thiazol-4-yl}-2,2-dimethylpropanoic acid	592
136AB	I-35A	AD-H		(5 <i>S</i>)-3-{2-[4-amino-2-{6-fluoro-1-[4-methylcyclohexylmethyl]-1 <i>H</i> -indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-thiazol-4-yl}-2,2-dimethylpropanoic acid	592
137AA	I-42A	Racemic C18		3-{2-[4-amino-2-{6-fluoro-1-[4-methylcyclohexylmethyl]-1 <i>H</i> -indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid	576
137AB	I-42A	Racemic C18		3-{2-[4-amino-2-{6-fluoro-1-[4-methylcyclohexylmethyl]-1 <i>H</i> -indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid	576
138B	I-73	(<i>R,R</i>)WHE LK-O 1		3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-cyclopropyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	616

139B	I-73	(R,R)WHE LK-O 1		600
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EXAMPLE 140A

3-(4-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropanoic acid



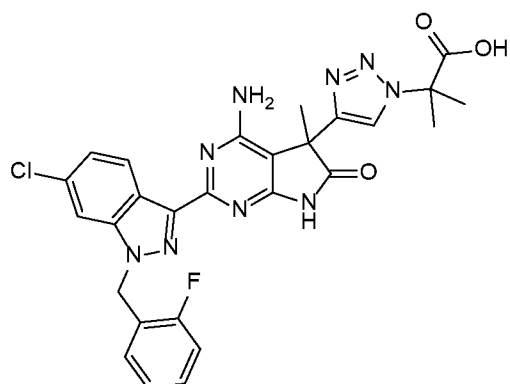
Step A- Ethyl 3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropanoate. A mixture containing **I-60** (460 mg, 1.273 mmol), **I-A15** (432 mg, 1.273 mmol) and potassium bicarbonate (637 mg, 6.36 mmol) in *t*-BuOH (10 ml) in a flask was stirred at 70 °C for 48 hours. The reaction was diluted with water and extracted with EtOAc (3X). The organic layers were combined, 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. *m/z* = 418 (M+1).

Step B- 3-(4-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropanoic acid. A flask, containing ethyl 3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1H-1,2,3-triazol-1-yl)-2,2-dimethylpropanoate (470 mg, 0.760 mmol) and LiOH (91 mg, 3.80 mmol) in a mixture of MeCN (5 ml) and water (5 ml) was stirred at 40 °C for 3 hours. The mixture was cooled to RT, diluted with EtOAc and aq. sat. KH₂PO₄, extracted with EtOAc, the organic layers were combined, washed with brine, dried over anhydr. MgSO₄, and filtered. The filtrate was concentrated *in*

vacuo. to afford the racemic title compound **Ex-140**. The racemic material was resolved using chiral SFC (CHIRALPAK[®] AD) to afford isomer **Ex-140A** (faster eluting) and isomer **Ex-140B** (slower eluting). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.73 (s, 1H), 11.25 (s, 1H), 8.69 (d, *J* = 8.7 Hz, 1H), 8.01 (d, *J* = 1.7 Hz, 1H), 7.91 (s, 1H), 7.36 (t, *J* = 7.0 Hz, 1H), 7.29 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.27 – 7.20 (m, 1H), 7.19 – 7.10 (m, 2H), 6.73 (s, 2H), 5.81 (s, 2H), 4.48 (s, 2H), 1.24 (s, 3H), 1.07 (d, *J* = 15.1 Hz, 6H), *m/z* = 590 (M+1).

EXAMPLE 141A

2-(4-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)-2-methylpropanoic acid



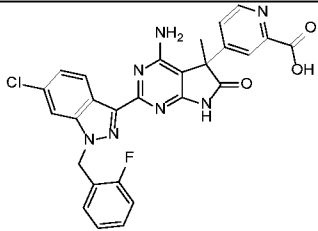
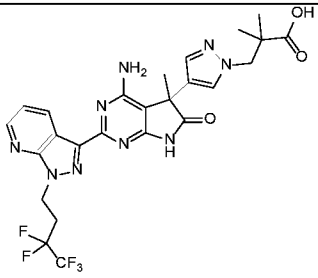
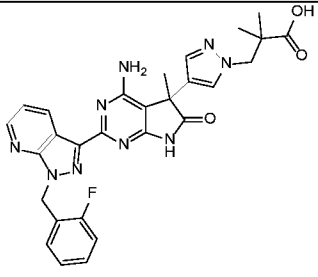
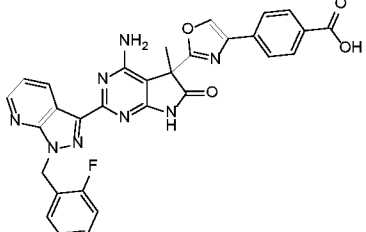
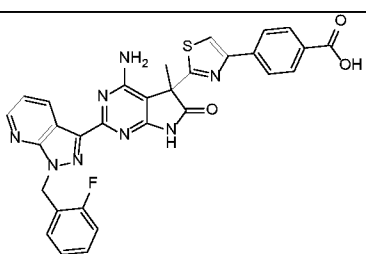
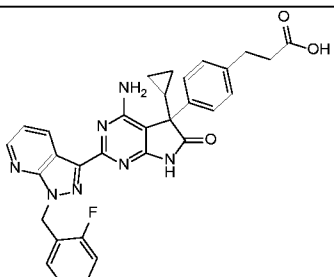
Ex-141A was prepared following essentially the same procedure described in **Ex-140A**, using **I-61** as starting material. The racemic material was resolved using chiral SFC (CHIRALCEL[®] OZ) to afford isomer **Ex-141A** (faster eluting) and isomer **Ex-141B** (slower eluting).

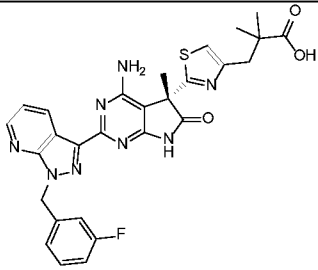
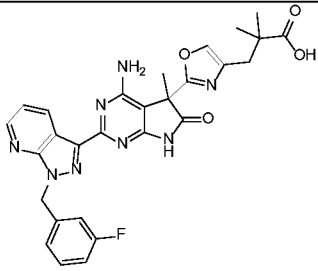
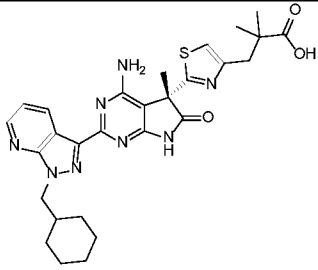
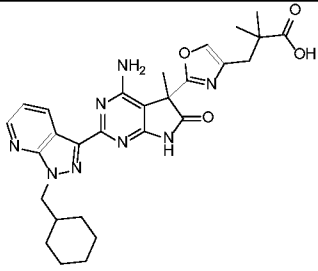
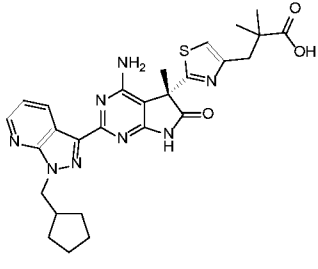
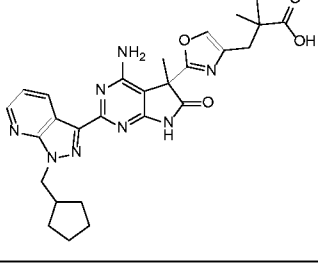
EXAMPLES 142B-219A

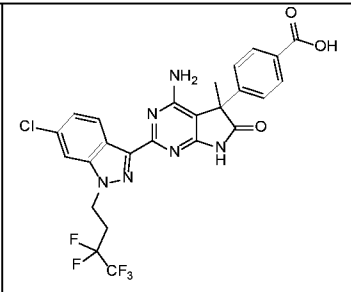
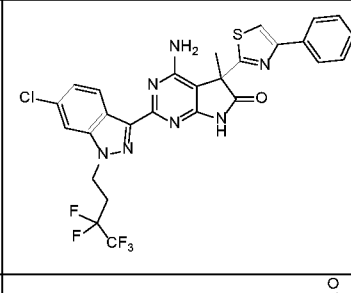
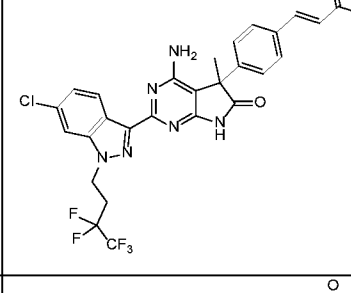
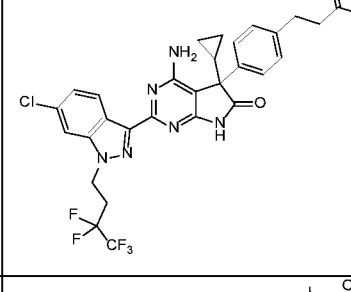
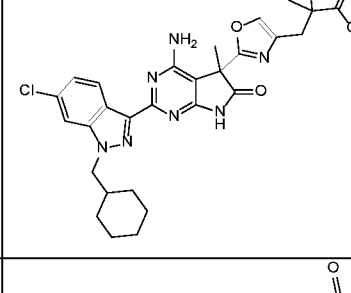
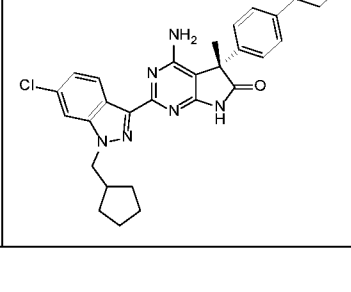
Using essentially the same procedure as described in Example **9B**, **Ex-10B** and **Ex-11B**, the following compounds in **Table 19** were prepared.

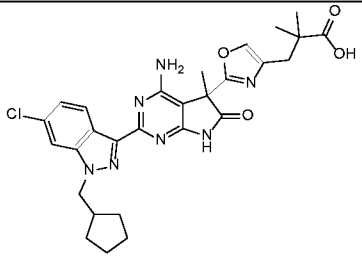
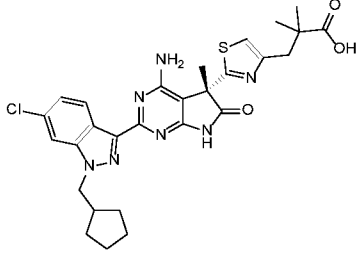
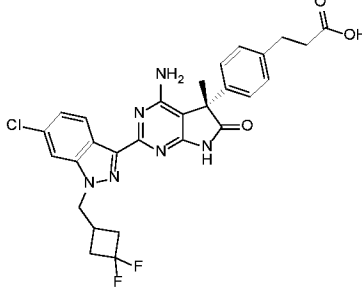
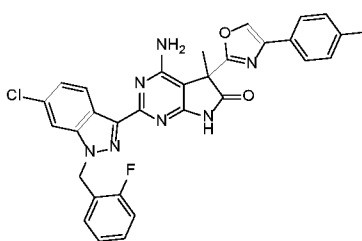
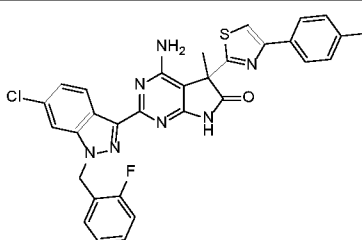
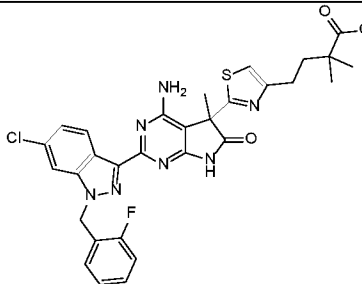
Table 19

Ex.	Int. SM	Structure	Name	<i>m/z</i> (M+1)
142B	I-65B		3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-thiazol-2-yl)-2,2-dimethylpropanoic acid	606

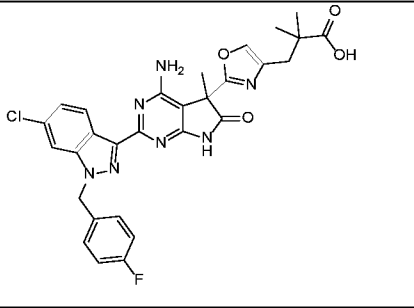
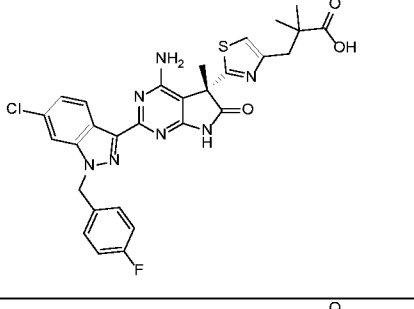
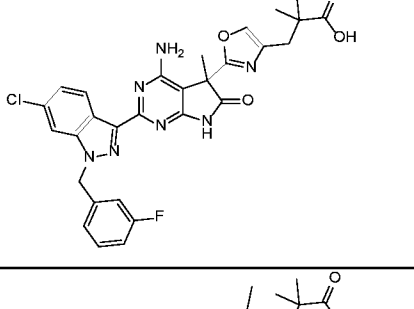
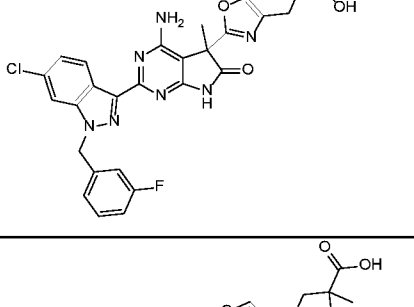
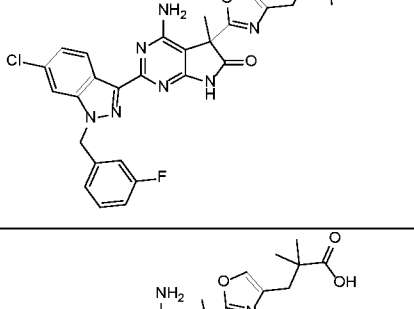
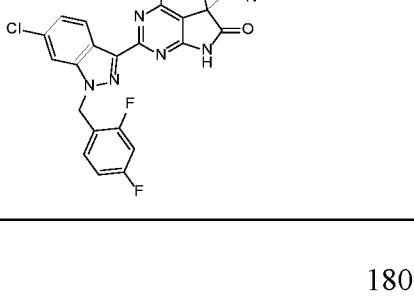
143B	I-74B		4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}pyridine-2-carboxylic acid	544
144A	I-63A		3-(4-{4-amino-5-methyl-6-oxo-2-[1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1H-pyrazol-1-yl)-2,2-dimethylpropanoic acid	594
145A	I-63A		3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1H-pyrazol-1-yl)-2,2-dimethylpropanoic acid	556
146A	I-53A		4-(2-{4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-oxazol-4-yl)benzoic acid	577
147A	I-58A		4-(2-{4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-thiazol-4-yl)benzoic acid	593
148A	I-75A		3-(4-{4-amino-5-cyclopropyl-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	564

149A	I-35A		(S)-3-(2-{4-amino-2-[1-(3-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid	573
150A	I-42A		3-(2-{4-amino-2-[1-(3-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	557
151A	I-35A		(S)-3-(2-{4-amino-2-[1-(cyclohexylmethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid	561
152A	I-42A		3-(2-{4-amino-2-[1-(cyclohexylmethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	545
153A	I-35A		(S)-3-(2-{4-amino-2-[1-(cyclopentylmethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid	547
154A	I-42A		3-(2-{4-amino-2-[1-(cyclopentylmethyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	531

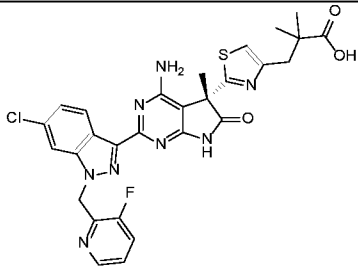
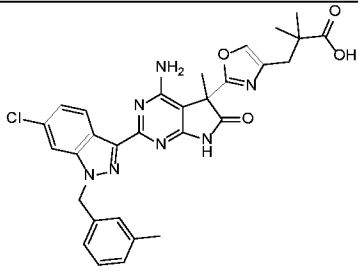
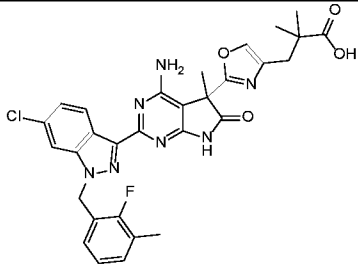
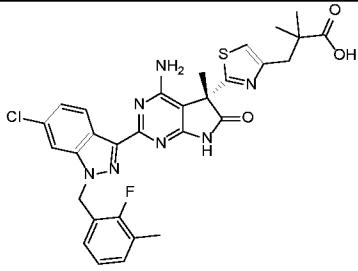
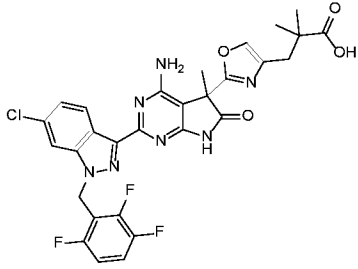
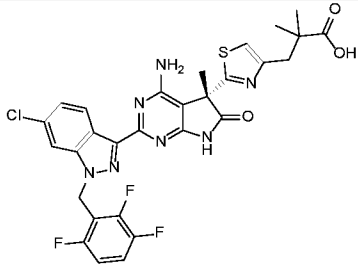
155B	I-48B		4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}benzoic acid	581
156A	I-58A		4-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-thiazol-4-yl)benzoic acid	664
157A	I-76A		(2 <i>E</i>)-3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)prop-2-enoic acid	607
158A	I-75A		3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1 <i>H</i> -indazol-3-yl]-5-cyclopropyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoic acid	635
159A	I-42A		3-(2-{4-amino-2-[6-chloro-1-(cyclohexylmethyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	578
160B	I-11B		(<i>S</i>)-3-(4-{4-amino-2-[6-chloro-1-(cyclopentylmethyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoic acid	545

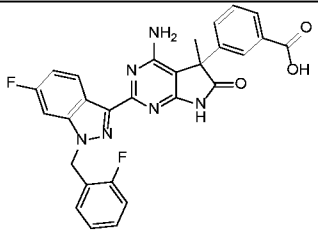
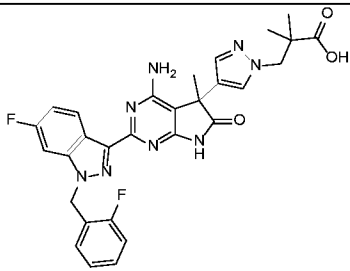
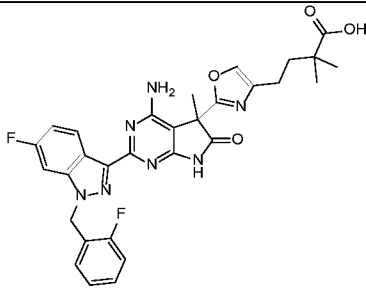
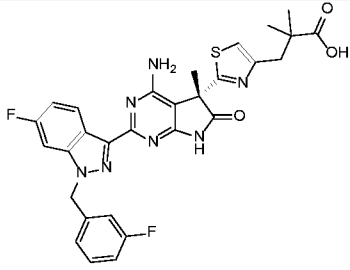
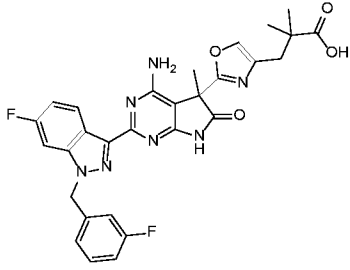
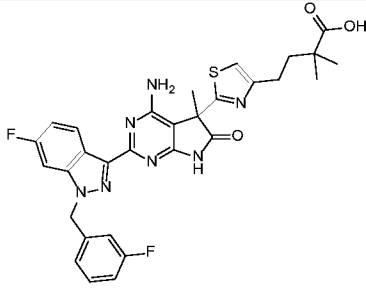
161A	I-42A		3-(2-{4-amino-2-[6-chloro-1-(cyclopentylmethyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	564
162A	I-35A		(<i>S</i>)-3-(2-{4-amino-2-[6-chloro-1-(cyclopentylmethyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid	580
163B	I-11B		(<i>S</i>)-3-{4-[4-amino-2-{6-chloro-1-[(3,3-difluorocyclobutyl)methyl]-1 <i>H</i> -indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]phenyl}propanoic acid	567
164A	I-53A		4-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)benzoic acid	610
165A	I-58A		4-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-thiazol-4-yl)benzoic acid	626
166A	I-59A		4-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylbutanoic acid	620

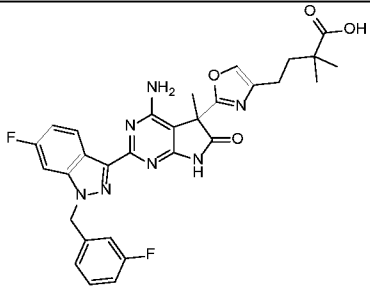
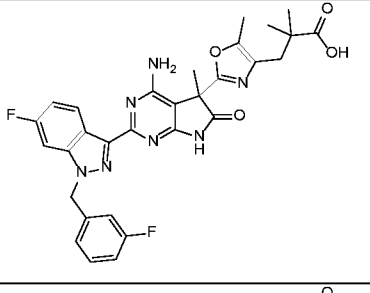
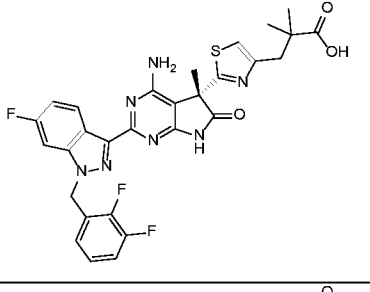
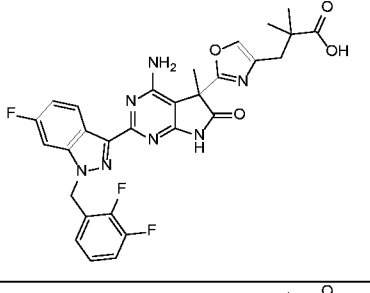
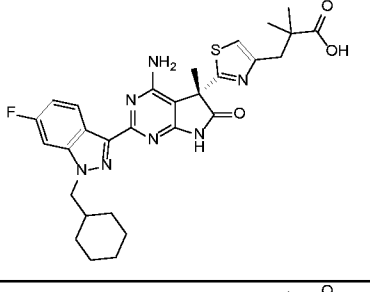
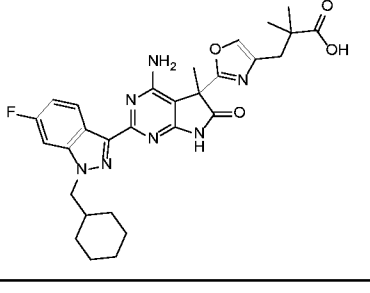
167B	I-55B		4-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylbutanoic acid	604
168B	I-66B		2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-benzoxazole-5-carboxylic acid	584
169B	I-37B		3-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}benzoic acid	543
170B	I-56B		3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-5-methyl-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	604
171A	I-63A		3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1 <i>H</i> -pyrazol-1-yl)-2,2-dimethylpropanoic acid	589
172A	I-57A		3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-D-alanine	577

173A	I-42A		3-(2-{4-amino-2-[6-chloro-1-(4-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	590
174A	I-35A		(<i>S</i>)-3-(2-{4-amino-2-[6-chloro-1-(4-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid	606
175A	I-42A		3-(2-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	590
176B	I-56B		3-(2-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-5-methyl-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	604
177B	I-55B		4-(2-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylbutanoic acid	604
178A	I-42A		3-(2-{4-amino-2-[6-chloro-1-(2,4-difluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	608

179A	I-35A		(S)-3-(2-({4-amino-2-[6-chloro-1-(2,4-difluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid	624
180A	I-42A		3-(2-({4-amino-2-[6-chloro-1-(2,3-difluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	608
181A	I-35A		(S)-3-(2-({4-amino-2-[6-chloro-1-(2,3-difluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid	624
182A	I-42A		3-(2-({4-amino-2-[6-chloro-1-(2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	608
183A	I-35A		(S)-3-(2-({4-amino-2-[6-chloro-1-(2,6-difluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid	624
184A	I-42A		3-{2-[4-amino-2-({6-chloro-1-[(3-fluoropyridin-2-yl)methyl]-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid	591

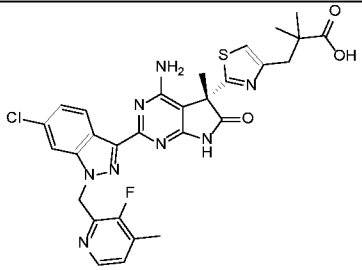
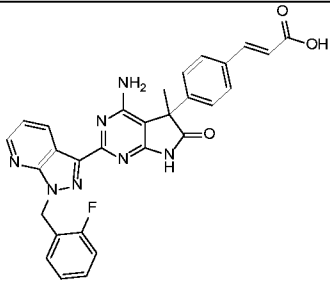
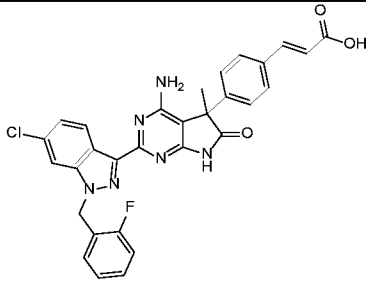
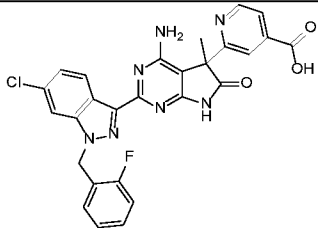
185A	I-35A		(S)-3-{2-[4-amino-2-{6-chloro-1-[(3-fluoropyridin-2-yl)methyl]-1H-indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl]-1,3-thiazol-4-yl}-2,2-dimethylpropanoic acid	607
186A	I-42A		3-(2-{4-amino-2-[6-chloro-1-(3-methylbenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	586
187A	I-42A		3-(2-{4-amino-2-[6-chloro-1-(2-fluoro-3-methylbenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	604
188A	I-35A		(S)-3-(2-{4-amino-2-[6-chloro-1-(2-fluoro-3-methylbenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid	620
189A	I-42A		3-(2-{4-amino-2-[6-chloro-1-(2,3,6-trifluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	626
190A	I-35A		(S)-3-(2-{4-amino-2-[6-chloro-1-(2,3,6-trifluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid	642

191B	I-37B		3-(4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)benzoic acid	527
192A	I-63A		3-(4-(4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)-1 <i>H</i> -pyrazol-1-yl)-2,2-dimethylpropanoic acid	573
193B	I-55B		4-(2-(4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)-1,3-oxazol-4-yl)-2,2-dimethylbutanoic acid	588
194A	I-35A		(<i>S</i>)-3-(2-(4-amino-2-[6-fluoro-1-(3-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid	590
195A	I-42A		3-(2-(4-amino-2-[6-fluoro-1-(3-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	574
196A	I-59A		4-(2-(4-amino-2-[6-fluoro-1-(3-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl)-1,3-thiazol-4-yl)-2,2-dimethylbutanoic acid	604

197B	I-55B		4-(2-{4-amino-2-[6-fluoro-1-(3-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylbutanoic acid	588
198B	I-56B		3-(2-{4-amino-2-[6-fluoro-1-(3-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-5-methyl-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	588
199A	I-35A		(<i>S</i>)-3-(2-{4-amino-2-[1-(2,3-difluorobenzyl)-6-fluoro-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid	608
200A	I-42A		3-(2-{4-amino-2-[1-(2,3-difluorobenzyl)-6-fluoro-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	592
201A	I-35A		(<i>S</i>)-3-(2-{4-amino-2-[1-(cyclohexylmethyl)-6-fluoro-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid	578
202A	I-42A		3-(2-{4-amino-2-[1-(cyclohexylmethyl)-6-fluoro-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	562

203B	I-34B		(2-{4-amino-2-[1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)acetic acid	514
204A	I-59A		4-(2-{4-amino-2-[1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylbutanoic acid	586
206B	I-55B		4-(2-{4-amino-2-[1-(2-fluorobenzyl)-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylbutanoic acid	571
207B	I-55B		4-{2-[4-amino-2-{6-chloro-1-[(3-fluoropyridin-2-yl)methyl]-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylbutanoic acid	605
208A	I-42A		3-(2-{4-amino-2-[6-chloro-1-(3,3-dimethylbutyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	566
209B	I-48B		4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}benzoic acid	543

210B	I-11B		(S)-3-(4-{4-amino-2-[1-(3,3-dimethylbutyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanoic acid	515
211A	I-63A		3-(4-{4-amino-2-[6-fluoro-1-(2-fluoro-3-methylbenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1H-pyrazol-1-yl)-2,2-dimethylpropanoic acid	587
212A	I-42A		3-(2-{4-amino-2-[6-fluoro-1-(2-fluoro-3-methylbenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	588
213A	I-42A		3-(2-{4-amino-2-[6-chloro-1-(2-fluoro-5-methylbenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	604
214A	I-35A		(S)-3-(2-{4-amino-2-[6-chloro-1-(2-fluoro-5-methylbenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid	620
215A	I-42A		3-(2-{4-amino-2-[6-chloro-1-((3-fluoro-4-methylpyridin-2-yl)methyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	605

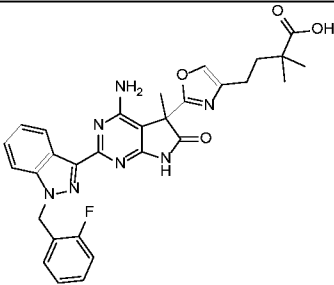
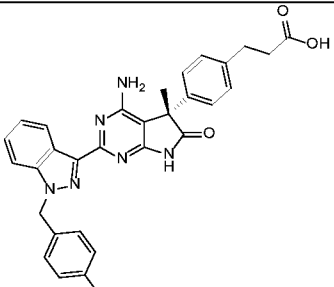
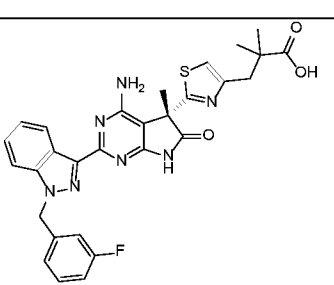
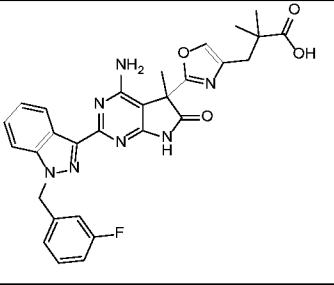
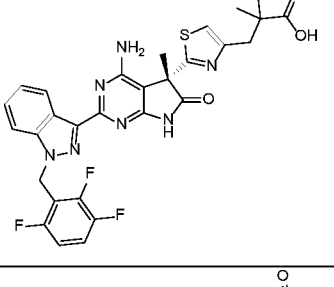
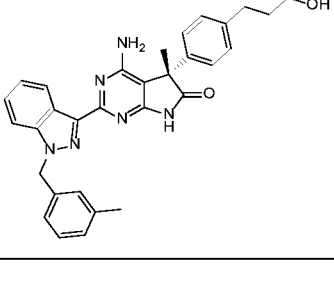
216A	I-35A		(S)-3-(2-{4-amino-2-[6-chloro-1-((3-fluoro-4-methylpyridin-2-yl)methyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid	621
217A	I-76A		(2E)-3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)prop-2-enoic acid	536
218A	I-76A		(2E)-3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)prop-2-enoic acid	509
219A	I-51A		2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}pyridine-4-carboxylic acid	544

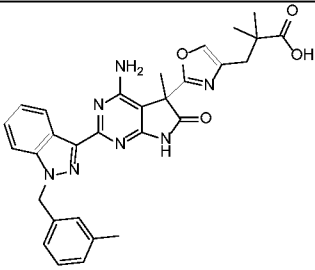
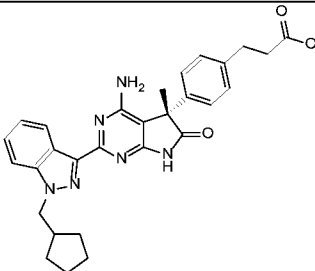
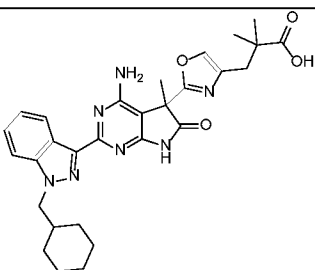
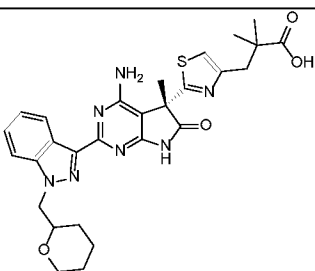
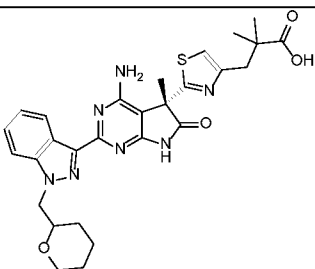
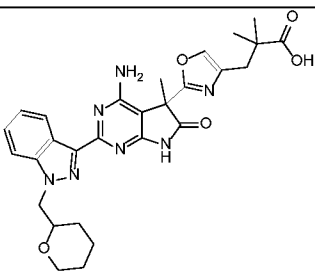
EXAMPLES 220B-233A

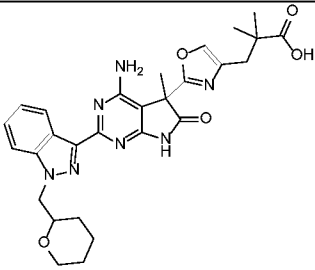
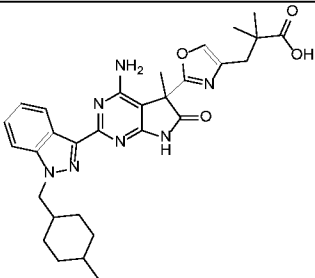
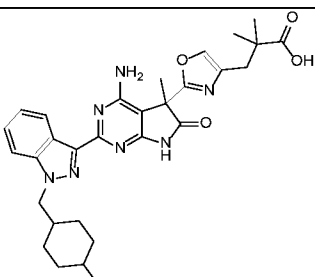
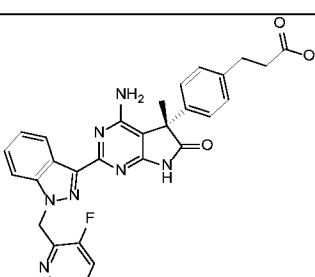
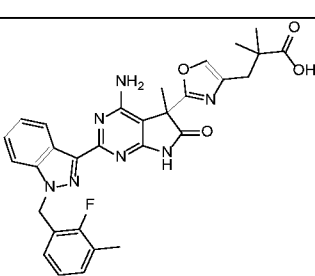
Using essentially the same procedure as described in Example 76B, the following compounds in Table 20 were prepared.

5 Table 20

Ex.	Int. SM/ Chiral Resolution Step / Column	Structure	Name	<i>m/z</i> (M+1)
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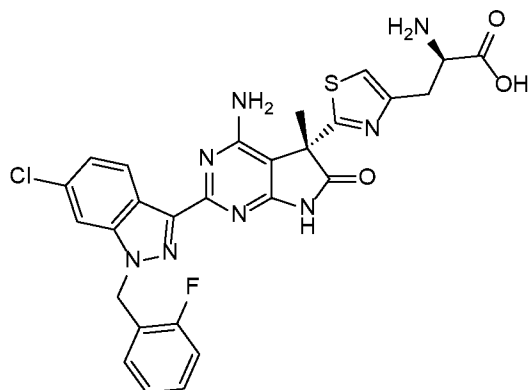
220B	I-55B/ -		4-(2-{4-amino-2-[1-(2-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylbutanoic acid	570
221B	I-11B/ -		(<i>S</i>)-3-(4-{4-amino-2-[1-(4-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoic acid	537
222A	I-35A/ -		(<i>S</i>)-3-(2-{4-amino-2-[1-(3-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid	572
223A	I-42A/ -		3-(2-{4-amino-2-[1-(3-fluorobenzyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	556
224A	I-35A/ -		(<i>S</i>)-3-(2-{4-amino-5-methyl-6-oxo-2-[1-(2,3,6-trifluorobenzyl)-1 <i>H</i> -indazol-3-yl]-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid	608
225B	I-11B/ -		(<i>S</i>)-3-(4-{4-amino-5-methyl-2-[1-(3-methylbenzyl)-1 <i>H</i> -indazol-3-yl]-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoic acid	533

226A	I-42A/ -		3-(2-{4-amino-5-methyl-2-[1-(3-methylbenzyl)-1 <i>H</i> -indazol-3-yl]-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	552
227B	I-11B/ -		(<i>S</i>)-3-(4-{4-amino-2-[1-(cyclopentylmethyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}phenyl)propanoic acid	511
228A	I-42A/ -		3-(2-{4-amino-2-[1-(cyclohexylmethyl)-1 <i>H</i> -indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	544
229AA	I-35A/ Step B/ IC		(5 <i>S</i>)-3-{2-[4-amino-5-methyl-6-oxo-2-{1-[tetrahydro-2 <i>H</i> -pyran-2-ylmethyl]-1 <i>H</i> -indazol-3-yl]-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-thiazol-4-yl}-2,2-dimethylpropanoic acid	562
229AB	I-35A/ Step B/ IC		(5 <i>S</i>)-3-{2-[4-amino-5-methyl-6-oxo-2-{1-[tetrahydro-2 <i>H</i> -pyran-2-ylmethyl]-1 <i>H</i> -indazol-3-yl]-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-thiazol-4-yl}-2,2-dimethylpropanoic acid	562
230AA	I-42A/ Step B/ IC		3-{2-[4-amino-5-methyl-6-oxo-2-{1-[tetrahydro-2 <i>H</i> -pyran-2-ylmethyl]-1 <i>H</i> -indazol-3-yl]-6,7-dihydro-5 <i>H</i> -pyrrolo[2,3- <i>d</i>]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid	546

230AB	I-42A/ Step B/ IC		3-{2-[4-amino-5-methyl-6-oxo-2-{1-[tetrahydro-2H-pyran-2-ylmethyl]-1H-indazol-3-yl}-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid	546
231AA	I-42A/ Step B/ Chiral Cellulose-SB		3-{2-[4-amino-5-methyl-2-{1-[4-methylcyclohexylmethyl]-1H-indazol-3-yl}-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid	558
231AB	I-42A/ Step B/ Chiral Cellulose-SB		3-{2-[4-amino-5-methyl-2-{1-[4-methylcyclohexylmethyl]-1H-indazol-3-yl}-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid	558
232B	I-11B/ -		(S)-3-{4-[4-amino-2-{1-(3-fluoropyridin-2-yl)methyl]-1H-indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl]phenyl}propanoic acid	538
233A	I-42A/-		3-(2-{4-amino-2-[1-(2-fluoro-3-methylbenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid	570

EXAMPLE 234B

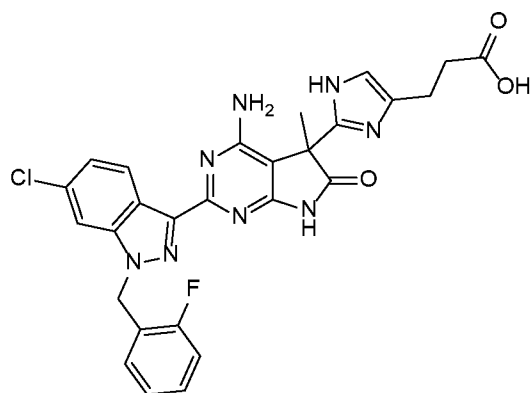
(S)-3-(2-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1,3-thiazol-4-yl)-D-alanine



Example 234B was prepared using essentially the same procedures to those described in example 77B, using **I-40B** as starting material and **I-47** as the bromoketone. ¹H NMR (300 MHz, CD₃OD): δ 8.48 (d, *J* = 8.7 Hz, 1H), 7.89 (s, 1H), 7.48 (s, 1H), 7.43-7.28 (m, 3H), 7.17-7.11 (m, 2H), 5.89 (s, 2H), 4.38 (dd, *J* = 7.2, 5.4 Hz, 1H), 3.51-3.32 (m, 2H), 2.00 (s, 3H); *m/z* = 593 (M + 1).

EXAMPLE 235B

3-(2-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1H-imidazol-4-yl)propanoic acid

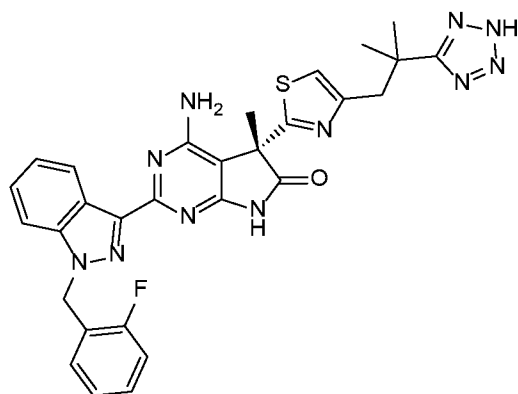


Step A- *tert*-Butyl 3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}-1-(4-methoxybenzyl)-1H-imidazol-4-yl)propanoate. A flask containing **I-A15** (136 mg, 0.45 mmol), **I-77** (180 mg, 0.38 mmol) and potassium bicarbonate (375 mg, 3.75 mmol) in *t*-BuOH (15 mL) was stirred for 16 h at 80 °C then concentrated *in vacuo*. The residue was purified by silica gel column chromatography with MeOH:DCM (0-10%) to afford the racemic title compound. The racemic material was resolved using Chiral HPLC (CHIRALPAK® IC) to afford isomer **A** (faster eluting) and isomer **B** (slower eluting).

Step B- 3-(2-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-imidazol-4-yl)propanoic acid. A flask containing *tert*-butyl 3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1-(4-methoxybenzyl)-1*H*-imidazol-4-yl)propanoate isomer **B** (70 mg, 0.095 mmol) and trifluoroacetic acid (3 mL) was stirred for 16 h at 100 °C then concentrated *in vacuo*. The residue was purified by reverse phase HPLC (ACN/water with 0.05% TFA modifier) to afford the title compound. ¹H NMR (300 MHz, CD₃OD) δ 8.51 (d, *J* = 8.7 Hz, 1H), 7.87 (s, 1H), 7.41-7.28 (m, 4H), 7.17-7.12 (m, 2H), 5.88 (s, 2H), 2.97 (t, *J* = 6.9 Hz, 2H), 2.71 (t, *J* = 6.9 Hz, 2H), 2.05 (s, 3H); *m/z* = 561 (*M* + 1).

EXAMPLE 236A

(*S*)-4-Amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5-{4-[2-methyl-2-(2*H*-tetrazol-5-yl)propyl]thiazol-2-yl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one



Step A- (*S*)-Ethyl 3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}thiazol-4-yl)-2,2-dimethylpropanoate. A flask, containing **I-A40** (130 mg, 0.49 mmol), **I-35A** (183 mg, 0.49 mmol) and potassium bicarbonate (97 mg, 0.97 mmol) in *t*-BuOH (3 mL), was stirred at 75 °C for 16 h then concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using MeOH:DCM (0-5%) to afford the title product. *m/z* = 600 (*M* + 1)

Step B- (*S*)-3-(2-{4-Amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}thiazol-4-yl)-2,2-dimethylpropanoic acid To a flask containing (*S*)-ethyl 3-(2{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}thiazol-4-yl)-2,2-dimethylpropanoate (225 mg, 0.38 mmol) in MeOH (5 mL) and water (2.5 mL) at RT was added LiOH (180 mg, 7.50 mmol). The mixture was stirred at RT for 16 h. To the mixture was added HCl (7.5 mL, 1 N), and the solid was collected by filtration, washed with water (20 mL) and dried in an oven to afford the title compound *m/z* = 572 (*M* + 1).

Step C- (S)-3-(2-{4-Amino-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}thiazol-4-yl)-2,2-dimethylpropanamide.

To a flask containing (S)-3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}thiazol-4-yl)-2,2-dimethylpropanoic acid (190 mg, 0.33 mmol) and di-*tert*-butyl dicarbonate (160 mg, 0.731 mmol) in DCM (3 mL) at RT was added pyridine (58 mg, 0.73 mmol) and the resulting mixture was stirred at RT for 2 h. To this was added ammonium bicarbonate (79 mg, 0.99 mmol) and the mixture was stirred for 16 h at RT. The reaction was diluted with water, extracted with EtOAc (3X) and the organic layers were combined, dried over anhydr. Na₂SO₄, filtered and the filtrate was concentrated *in vacuo* to dryness. To the residue was added dichloromethane (4 mL) and TFA (2 mL). The mixture was stirred for 2 h at RT before water (10 mL) was added, and the pH of the mixture was adjusted to pH=7 with NaHCO₃. The resulting mixture was extracted with DCM (3 X), the organic layers were combined, dried over anhydr. Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using MeOH:DCM (0-5%) to afford the title product *m/z* = 571 (M + 1).

Step D- (S)-3-(2-{4-Amino-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}thiazol-4-yl)-2,2-dimethylpropanenitrile.

To a flask, containing (S)-3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}thiazol-4-yl)-2,2-dimethylpropanamide (180 mg, 0.32 mmol) and pyridine (0.5 mL, 6.18 mmol) in DCM (5 mL) at 0 °C was added dropwise TFAA (0.5 mL, 3.54 mmol). The mixture was stirred for 1 h at RT before MeOH (20 mL) was added and the mixture was concentrated *in vacuo*. The residue was diluted with water, and extracted with EtOAc (3 X). The organic layers were combined, dried over anhydr. Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using MeOH:DCM (0-5%) to afford the title product *m/z* = 553 (M + 1).

Step E- (S)-4-Amino-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5-{4-[2-methyl-2-(2H-tetrazol-5-yl)propyl]thiazol-2-yl}-5H-pyrrolo[2,3-d]pyrimidin-6(7H)-one.

A sealed tube containing (S)-3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}thiazol-4-yl)-2,2-dimethylpropanenitrile (100 mg, 0.181 mmol), sodium azide (118 mg, 1.81 mmol) and ammonium chloride (97 mg, 1.81 mmol) in DMA (3 mL) was stirred at 120 °C for 16 h. The resulting mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was then purified by reverse phase HPLC (ACN/water with 0.05% NH₄HCO₃ modifier) to afford the title compound **Ex-236A**. ¹H NMR (300 MHz,

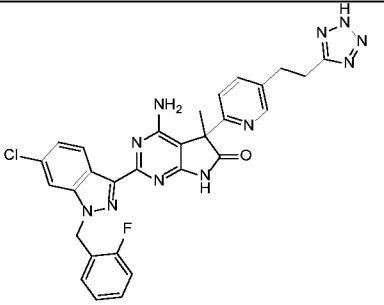
CD₃OD) δ 8.69 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.44 (dd, J = 7.5, 7.5 Hz, 1H), 7.31-7.26 (m, 2H), 7.16-7.04 (m, 4H), 5.81 (s, 2H), 3.22 (d, J = 6.6 Hz, 2H), 1.76 (s, 3H), 1.52 (s, 3H), 1.48 (s, 3H); m/z = 596 (M+1).

- 5 Using essentially the same procedure as described in **Ex-112B** and **Ex-236A**, the following compounds in **Table 20** were prepared.

Table 20

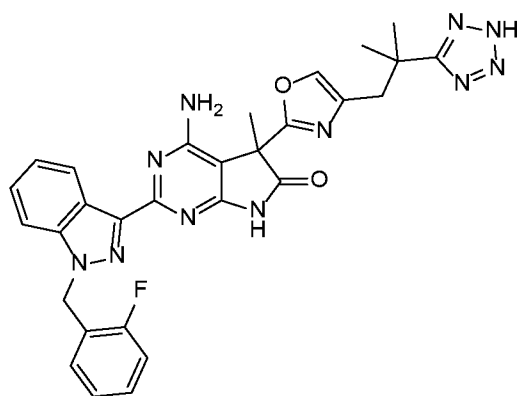
Ex.	Int. SM/ Chiral Resolution Step / Column	Structure	Name	m/z (M+1)
237B	I-11B/ -		(S)-4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-5-{4-[2-(2H-tetrazol-5-yl)ethyl]phenyl}-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	633
238A	I-35A/ -		(S)-4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5-{4-[2-methyl-2-(2H-tetrazol-5-yl)propyl]-1,3-thiazol-2-yl}-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	630
239A	I-42A/ -		4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5-{4-[2-methyl-2-(2H-tetrazol-5-yl)propyl]-1,3-oxazol-2-yl}-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	614
240B	I-11B/ -		(S)-4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-5-{4-[2-(2H-tetrazol-5-yl)ethyl]phenyl}-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	562

241A	I-35A/ -		(S)-4-amino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-methyl-5-{4-[2-methyl-2-(2H-tetrazol-5-yl)propyl]-1,3-thiazol-2-yl}-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	597
242B	I-11B/ -		(S)-4-amino-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5-{4-[2-(2H-tetrazol-5-yl)ethyl]phenyl}-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	561
243A	I-51A/ -		5-[4-(2H-tetrazol-5-yl)pyridin-2-yl]-4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	568
244A	I-78A/ -		5-{4-[(2H-tetrazol-5-yl)methyl]phenyl}-4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	581
245B	I-11B/ -		(S)-5-{4-[2-(2H-tetrazol-5-yl)ethyl]phenyl}-4-amino-2-{1-[(3-fluoropyridin-2-yl)methyl]-1H-indazol-3-yl}-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	562
246A	I-62/Step D/ IA		5-{5-[2-(2H-tetrazol-5-yl)ethyl]pyridin-2-yl}-4-amino-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	562

247A	I-62/Step D/ IA		5-{5-[2-(2H-tetrazol-5-yl)ethyl]pyridin-2-yl}-4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	596
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EXAMPLE 248B

4-Amino-2-[1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5-{4-[2-methyl-2-(2H-tetrazol-5-yl)propyl]oxazol-2-yl}-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one

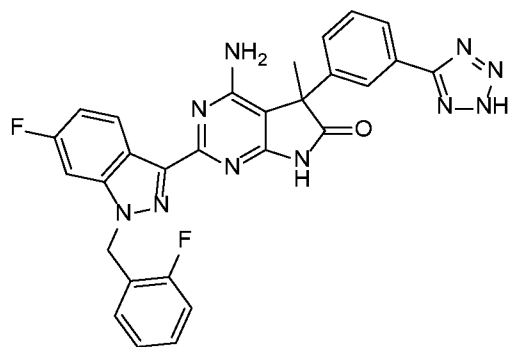


5

A flask containing **Ex-239A** (60 mg, 0.098 mmol) and palladium on carbon (80 mg, 0.068 mmol, 10 w%) in MeOH (2 mL) was evacuated and flushed (3X) with nitrogen, followed by flushing with hydrogen. The mixture was stirred for 5 h at RT under an atmosphere of hydrogen (1.5 atm). The palladium on carbon was filtered out and washed with MeOH (3 X), EtOAc (3 X), and DCM (3 X). The combined filtrate was concentrated *in vacuo*. The residue was then purified by reverse phase HPLC (ACN/water with 0.05% NH₄HCO₃ modifier) to afford the title compound ¹H NMR (300 MHz, CD₃OD) δ 8.68 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.41 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.32-7.23 (m, 2H), 7.14-7.00 (m, 4H), 5.78 (s, 2H), 2.91 (d, *J* = 8.7 Hz, 2H), 1.83 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H); *m/z* = 580 (*M* + 1).

15 **EXAMPLE 249B**

4-Amino-2-[6-fluoro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5-[3-(1H-tetrazol-5-yl)phenyl]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one



Step A- 3-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}benzonitrile. A flask containing **I-A23** (126 mg, 0.44 mmol), **I-69B** (98 mg, 0.37 mmol) and potassium bicarbonate (110 mg, 1.10 mmol) in *t*-BuOH (1.8 mL) was stirred at 80 °C for 16 h. The mixture was then concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using (EtOAc:EtOH 3:1) :
 5 Hexane (0-30%) to afford the title product.

Step B- 4-Amino-2-[6-fluoro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5-[3-(1H-tetrazol-5-yl)phenyl]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one: To a flask containing
 10 3-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}benzonitrile (120 mg, 0.24 mmol) in toluene (1 mL) was added dibutyltin oxide (6.0 mg, 0.02 mmol) and TMS azide (0.06 mL, 0.47 mmol). The resulting mixture was stirred at 130 °C for 2 days, and then concentrated *in vacuo*. The residue was purified by reverse phase HPLC (ACN/water with 0.05% formic acid modifier) to afford the title
 15 compound **Ex-249B**. ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.15 (s, 1H), 8.74 (dd, *J* = 10 Hz, 5 Hz, 1H), 7.95-7.88 (m, 2H), 7.68 (dd, *J* = 10 Hz, 5 Hz, 1H), 7.49-7.08 (m, 7H), 6.57 (br s, 2H), 5.77 (s, 2H), 1.83 (s, 3H); *m/z* = 551 (*M* + 1).

Using essentially the same procedure described in Example **249B**, the following compounds in
 20 **Table 21** were prepared

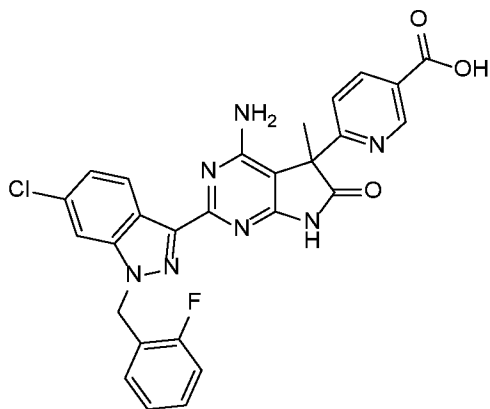
Table 21

Ex.	Int. SM/ Chiral Resolution Step / Column	Structure	Name	<i>m/z</i> (<i>M</i> +1)
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250B	I-70B/ -		4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5-[4-(1H-tetrazol-5-yl)phenyl]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	551
251B	I-69/ Step B/ AS		4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1H-indazol-3-yl]-5-methyl-5-[3-(1H-tetrazol-5-yl)phenyl]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	605
252B	I-69/ Step B/ AS		4-amino-5-methyl-2-[1-(3,3,4,4,4-pentafluorobutyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-[3-(2H-tetrazol-5-yl)phenyl]-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	572
253A	I-72/ Step A / IA		5-[6-(2H-tetrazol-5-yl)pyridin-2-yl]-4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one	568

EXAMPLE 254A

6-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}pyridine-3-carboxylic acid



5

Step A - 6-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}nicotinonitrile. A flask containing **I-71A** (89 mg,

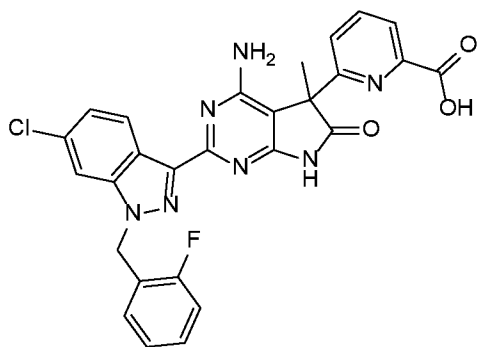
0.33 mmol), **I-A15** (100 mg, 0.33 mmol) and potassium bicarbonate (49 mg, 0.49 mmol) in *t*-BuOH (5 mL) was stirred for 16 h at 70 °C, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography with MeOH:DCM (0-10%) to afford the title compound.

- 5 **Step B- Methyl 6-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}nicotinate.** To a flask containing 6-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}nicotinonitrile (120 mg, 0.23 mmol) in MeOH (10 mL) at RT was added dropwise sulfurous dichloride (3 mL). The resulting mixture was stirred for 16 h at 80 °C then
10 concentrated *in vacuo*. To the residue was added 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 purified by silica gel column chromatography with MeOH:DCM (0-10%) to afford the title compound.

- Step C- 6-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-**
15 **dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}nicotinic acid.** A flask containing methyl 6-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}nicotinate (90 mg, 0.16 mmol), lithium hydroxide (1.6 mL, 1 M in water, 1.6 mmol) in MeOH (5 mL) was stirred for 16 h at RT, and then concentrated *in vacuo*. Water (3 mL) and hydrogen chloride (1 N, 1.6 mL) were added. The resulting solid was
20 collected by filtration and washed with water (3 X). The residue was purified by reverse phase HPLC (ACN/water with 0.05% TFA modifier) to afford the title compound **Ex-254A**. ¹H NMR (300 MHz, CD₃OD) δ 9.11 (d, *J* = 1.5 Hz, 1H), 8.67 (d, *J* = 8.7 Hz, 1H), 8.28 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.64 (s, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.37-7.29 (m, 1H), 7.25 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.18-7.07 (m, 3H), 5.77 (s, 2H), 1.92 (s, 3H); *m/z* = 544 (*M* + 1).

25 **EXAMPLE 255A**

6-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}picolinic acid



Step A- 6-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}picolinonitrile. A flask containing **I-72** (430 mg, 1.60 mmol), **I-A15** (510 mg, 1.68 mmol) and potassium bicarbonate (802 mg, 8.01 mmol) in *t*-BuOH (10 mL) was stirred at 70 °C for 16 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with MeOH:DCM (0-10%) to afford the title racemic compound. The racemic material was resolved using Chiral HPLC (CHIRALPAK® IA) to afford isomer **A** (faster eluting) and isomer **B** (slower eluting).

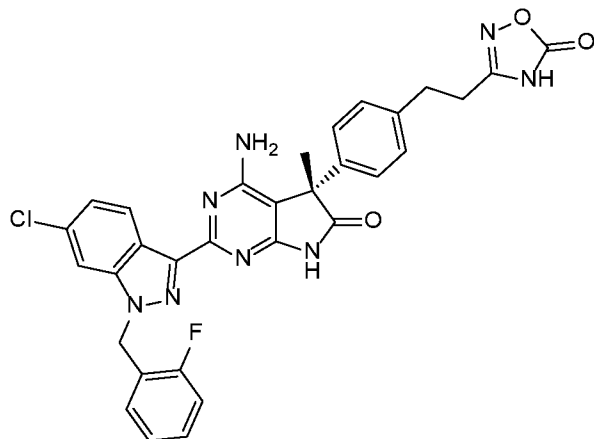
Step B- Methyl 6-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}picolinate. To a flask containing 6-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}picolinonitrile isomer **A** (40 mg, 0.076 mmol) in MeOH (10 mL) at RT was added dropwise sulfurous dichloride (1 mL, 13.70 mmol). The resulting mixture was stirred for 16 h at 80 °C, and then the mixture was concentrated *in vacuo*. The residue was diluted with 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 purified by silica gel column chromatography with MeOH:DCM (0-10%) to afford the title compound.

Step C- 6-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}picolinic acid. A flask containing methyl 6-(4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)picolinate (40 mg, 0.072 mmol) and lithium hydroxide (69 mg, 2.87 mmol) in a mixture of water (1.5 mL): THF (1.5 mL) was stirred for 16 h at RT. To this was added hydrochloric acid (28.7 mL, 0.1 N). The solid was collected by filtration, washed with water (2 x 5 mL), and dried in an oven to afford the title compound **Ex-255A**. ¹H NMR (300 MHz, CD₃OD) δ 8.65 (d, *J* = 8.7 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.99 (dd, *J* = 7.8, 7.8 Hz, 1H),

7.71 (d, $J = 7.8$ Hz, 1H), 7.64 (s, 1H), 7.36-7.22 (m, 2H), 7.17-7.06 (m, 3H), 5.76 (s, 2H), 1.91 (s, 3H); $m/z = 544$ ($M + 1$).

EXAMPLE 256B

(S)-4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5-{4-[2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)ethyl]phenyl}-5,7-dihydro-6H-pyrrolo[2,3-*d*]pyrimidin-6-one



Step A- (S)-3-(4-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamide. To a flask containing **Ex-47B** (1.0 g, 1.58 mmol) in DMF (10 mL) was added di(1H-imidazol-1-yl)methanone (1.28 g, 7.88 mmol). The mixture was stirred at RT for 30 min before ammonium chloride (0.17 g, 3.15 mmol) was added. The resulting mixture was stirred at RT for 16 h, then diluted with water, and extracted with EtOAc (3 X). The organic layers were combined, dried over anhydr. Na_2SO_4 , filtered, and the filtrate was concentrated *in vacuo* to dryness. The residue was purified by silica gel chromatography using MeOH:DCM (0-5%) to afford the title product, $m/z = 570$ ($M + 1$).

Step B- (S)-3-(4-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanenitrile. To a flask containing (S)-3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamide (0.8 g, 1.40 mmol) and pyridine (0.5 mL, 6.18 mmol) in DCM (5 mL) at 0 °C, was added dropwise TFAA (0.5 mL, 3.54 mmol). The mixture was stirred at RT for 1 h. The mixture was diluted with MeOH and concentrated *in vacuo*. The residue was diluted with water, extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with MeOH:DCM (0-5%) to afford the title compound. $m/z = 552$ ($M + 1$).

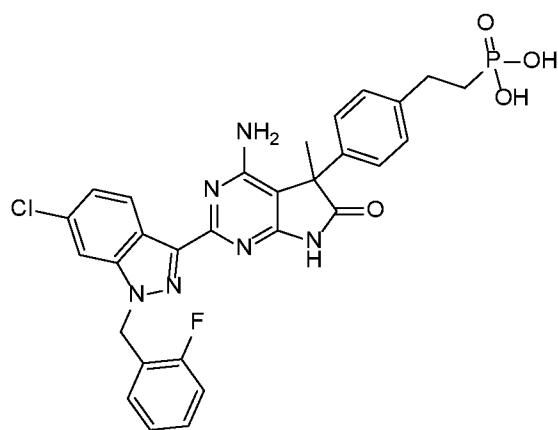
Step C- (S)-3-(4-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-N-hydroxypropanimidamide. A flask,

containing (S)-3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)propanenitrile (150 mg, 0.272 mmol) and aqueous hydroxylamine (7.5 mL, 0.272 mmol, 50%) in EtOH (7.5 mL) was stirred at 30 °C for 16 h. The mixture was concentrated *in vacuo* and the residue was lyophilized to afford the title compound $m/z = 585$ (M + 1).

Step D- (S)-3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenethyl)-1,2,4-oxadiazol-5(4H)-one. A flask containing (S)-3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)-N-hydroxypropanimidamide (120 mg, 0.21 mmol), di(1H-imidazol-1-yl)methanone (332 mg, 2.05 mmol,) in THF (12 mL) was stirred at RT for 16 h and at 50 °C for 24 h. The mixture was concentrated *in vacuo*, and aq. sat. NaHCO₃ was added to the residue. The mixture was 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 purified by silica gel column chromatography with MeOH:DCM (0-10%) then by reverse phase HPLC (ACN/water with 0.05% TFA modifier) to afford the title compound **Ex-256B**. ¹H NMR (300 MHz, CD₃OD) δ 8.65 (d, $J = 8.7$ Hz, 1H), 7.62 (s, 1H), 7.33-7.21 (m, 6H), 7.15-7.04 (m, 3H), 4.84 (s, 2H), 2.94 (t, $J = 7.2$ Hz, 2H), 2.78 (t, $J = 7.2$ Hz, 2H), 1.98 (s, 3H); $m/z = 611$ (M + 1).

EXAMPLE 257A

[2-(4-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenyl)ethyl]phosphonic acid



Step A- 4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-[4-(diethoxymethyl)phenyl]-5-methyl-5H-pyrrolo[2,3-d]pyrimidin-6(7H)-one. A flask

containing **I-A15** (200 mg, 0.66 mmol), **I-49** (228 mg, 0.66 mmol) and potassium bicarbonate

(79 mg, 0.79 mmol) in *t*-BuOH (4 mL) was stirred at 70 °C for 16 h. The reaction mixture was concentrated *in vacuo* to dryness to afford the title compound. $m/z = 601$ ($M + 1$).

Step B- 4-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}benzaldehyde. To a flask containing 4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-[4-(diethoxymethyl)phenyl]-5-methyl-5*H*-pyrrolo[2,3-*d*]pyrimidin-6(7*H*)-one (250 mg, 0.25 mmol) in DCM (10 ml) at RT was added TFA (1 mL) dropwise. The resulting mixture was stirred for 16 h at RT then concentrated *in vacuo*, diluted with EtOAc, washed with aq. sat. NaHCO₃, dried over anhydr. Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with MeOH:DCM (0-10%) to afford the title compound. $m/z = 527$ ($M + 1$).

Step C- Diethyl 4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}styrylphosphonate. A flask containing 4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}benzaldehyde (120 mg, 0.228 mmol), diethyl ((triphenylphosphoranylidene)methyl)phosphonate (470 mg, 1.139 mmol), (prepared following *J. Org. Chem.*, **1996**, *61* (22), 7697) in a DMF (2 mL): toluene (10 mL) mixture was stirred at 90 °C for 16 h. The reaction was diluted with EtOAc, 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 (0-10%) to afford the title compound. $m/z = 661$ ($M + 1$).

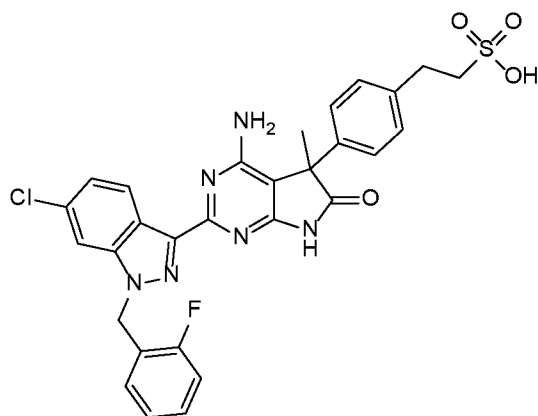
Step D- Diethyl 4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenethylphosphonate. A flask, containing diethyl 4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}styrylphosphonate (65 mg, 0.098 mmol), sodium acetate (40 mg, 0.492 mmol) and 4-methylbenzenesulfonylhydrazide (55 mg, 0.295 mmol) in a 1,2-dimethoxyethane (20 mL): water (2 mL) mixture was stirred at 80 °C for 16 h. The reaction was diluted with water, 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 purified by silica gel column chromatography with MeOH:DCM (0-10%) to afford racemic title product. The racemic material was resolved using Chiral HPLC (CHIRALPAK® IA) to afford isomer **A** (faster eluting) and isomer **B** (slower eluting). $m/z = 663$ ($M + 1$).

Step E- 4-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenethylphosphonic acid. To a flask containing

diethyl 4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenethylphosphonate isomer **A** (25 mg, 0.038 mmol) in DCM (20 mL) at 0 °C was added dropwise bromotrimethylsilane (2 mL). The resulting mixture was stirred for 5 days at RT. The mixture was concentrated *in vacuo*, and diluted with MeOH (2 mL). The resulting mixture stirred at RT for 30 min. The mixture was then concentrated *in vacuo*, and the residue was purified by reverse phase HPLC (ACN/water with 0.05% TFA modifier) to afford the title compound **Ex-257A**. ¹H NMR (300 MHz, CD₃OD) δ 8.56 (d, *J* = 8.7 Hz, 1H), 7.79 (s, 1H), 7.43-7.21 (m, 6H), 7.19-7.08 (m, 3H), 5.82 (s, 2H), 2.91-2.82 (m, 2H), 1.99-1.88 (m, 2H), 1.81 (s, 3H); *m/z* = 607 (*M* + 1).

EXAMPLE 258B

2-(4-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)ethanesulfonic acid



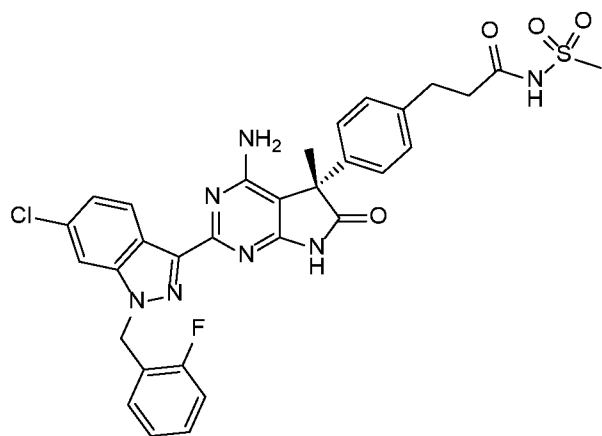
Step A- Ethyl 2-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-

oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)ethenesulfonate. To a flask under an inert atmosphere of nitrogen, containing ethyl (diethoxyphosphoryl) methanesulfonate (3.46 g, 13.28 mmol) in THF (70 mL) at -78 °C was added dropwise *n*-butyllithium (4.3 mL, 10.63 mmol, 2.5 M in hexane). The resulting mixture was stirred for 30 min at -78 °C before 4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}benzaldehyde (700 mg, 1.33 mmol) was added, and the resulting mixture was stirred for 16 h at RT. The reaction was quenched by the addition of aq. sat. NH₄Cl, 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 purified by silica gel column chromatography with MeOH:DCM (0-10%) to afford the title compound *m/z* = 633 (*M* + 1).

Step B- 2-(4-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)ethanesulfonic acid. A flask, containing ethyl 2-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)ethenesulfonate (750 mg, 1.19 mmol), sodium acetate (1.46 g, 17.77 mmol), 4-methylbenzenesulfonhydrazide (2.20 mg, 11.85 mmol) in a 1,2-dimethoxyethane (100 mL): water (20 mL) mixture was stirred at 80 °C for 6 h. The reaction was diluted with water, extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by reverse phase HPLC (ACN/water) to afford the title racemic compound **Ex-258**. The racemic material was resolved using chiral SFC (CHIRALPAK[®] IC) to afford isomer **Ex-258A** (faster eluting) and isomer **Ex-258B** (slower eluting). ¹H NMR (300 MHz, CD₃OD) δ 8.71 (d, *J* = 8.7 Hz, 1H), 7.68 (d, *J* = 1.5 Hz, 1H), 7.41-7.30 (m, 6H), 7.27-7.10 (m, 3H), 5.81 (s, 2H), 3.13-3.00 (m, 4H), 1.89 (s, 3H); *m/z* = 607 (*M* + 1).

EXAMPLE 259B

(*S*)-3-(4-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-*N*-(methylsulfonyl)propanamide

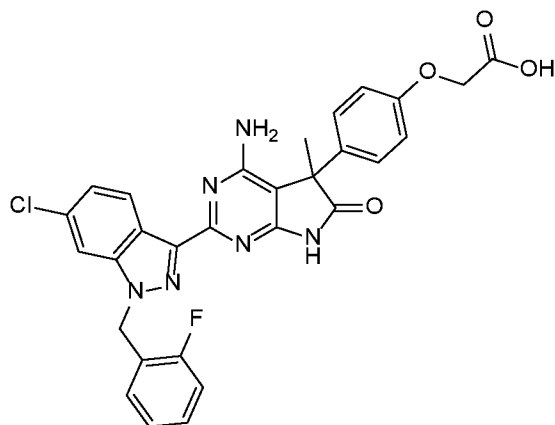


A flask containing **Ex-47B** (100 mg, 0.17 mmol), 4-dimethylaminopyridine (26 mg, 0.21 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (47 mg, 0.24 mmol) in DMF (16 mL) was stirred at RT for 30 min before methanesulfonamide (50 mg, 0.52 mmol) was added. The resulting mixture was stirred for 16 h at RT. The reaction was quenched by the addition of water, and extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with MeOH:DCM (0-8%). The residue was purified by reverse phase HPLC (ACN/water with 0.05% NH₄HCO₃ modifier) to afford the title compound **Ex-259B**. ¹H NMR (CD₃OD, 400 MHz): δ 8.71 (d, *J* = 8.8 Hz, 1H), 7.68 (s, 1H),

7.39-7.26 (m, 6H), 7.20-7.11 (m, 3H), 5.81 (s, 2H), 3.06 (s, 3H), 2.95 (t, $J = 7.2$ Hz, 1H), 2.59 (t, $J = 7.2$ Hz, 2H), 1.89 (s, 3H); $m/z = 648$ ($M + 1$).

EXAMPLE 260A

(4-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}phenoxy)acetic acid



Step A- 4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(4-methoxyphenyl)-5-methyl-5H-pyrrolo[2,3-d]pyrimidin-6(7H). A flask, containing **I-A15** (200 mg, 0.59 mmol), **I-50A** (161 mg, 0.59 mmol) and potassium bicarbonate (177 mg, 1.77 mmol) in *t*-BuOH (5 mL) was stirred at 75 °C for 16 h. The reaction was quenched by the addition of brine, 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 purified by silica gel column chromatography with MeOH:DCM (0-10%) to afford the title compound $m/z = 529$ ($M + 1$).

Step B- 4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(4-hydroxyphenyl)-5-methyl-5H-pyrrolo[2,3-d]pyrimidin-6(7H)-one. In a flask containing 4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-(4-methoxyphenyl)-5-methyl-5H-pyrrolo[2,3-d]pyrimidin-6(7H) (255 mg, 0.48 mmol), and tribromoborane (1 mL) in DCM (5 mL) at 0 °C. The resulting mixture was stirred at RT for 16 h. The reaction was quenched by the addition of ice water. The pH of the resulting mixture was adjusted to pH 8 with NaHCO₃, and the resulting mixture was 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 dissolved with hydrobromic acid (40%, 8 mL), and stirred for 16 h at 80 °C. The reaction was poured into ice water. The pH of the resulting solution was adjusted to pH 8 with NaHCO₃. 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 purified by silica gel

column chromatography with MeOH:DCM (0-10%) to afford the title compound $m/z = 515$ ($M + 1$).

Step C- Ethyl 2-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenoxy)acetate. To a flask wrapped in

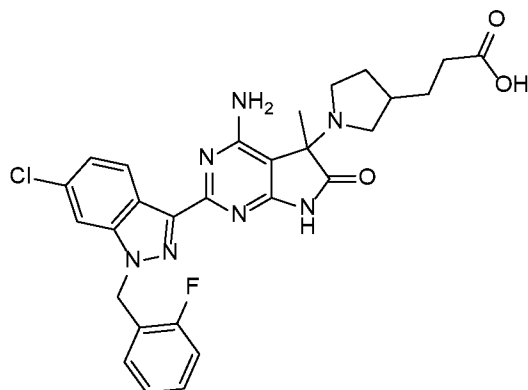
aluminum foil, were placed 4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-(4-hydroxyphenyl)-5-methyl-5*H*-pyrrolo[2,3-*d*]pyrimidin-6(7*H*)-one (80 mg, 0.16 mmol), silver carbonate (880 mg, 3.20 mmol), and ethyl 2-bromoacetate (7 mL) in acetonitrile (80 mL). The mixture was stirred at 80 °C for 16 h. The solid was filtered out and washed with dimethyl sulfoxide (3 X). The filtrate was concentrated *in vacuo*. The residue was purified by reverse phase HPLC (ACN/water with 0.05% NH_4HCO_3 modifier) to afford the title compound. $m/z = 601$ ($M + 1$).

Step D- 2-(4-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenoxy)acetic acid. A flask containing ethyl 2-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-

pyrrolo[2,3-*d*]pyrimidin-5-yl}phenoxy)acetate (55 mg, 0.09 mmol) and lithium hydroxide monohydrate (110 mg, 2.62 mmol) in a mixture of THF (4 mL): water (4 mL): MeOH (2 mL) was stirred at RT for 16 h. The resulting mixture was concentrated *in vacuo*. The residue was purified by reverse phase HPLC (ACN/water with 0.05% NH_4HCO_3 modifier). The fractions were combined and concentrated *in vacuo*. The pH of the resulting solution was adjusted to pH 4 with hydrochloric acid (1 N). The solid was collected by filtration, washed with water (2 X), and dried in an oven to afford the title product **Ex-260A**. ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 13.01 (brs, 1H), 11.07 (s, 1H), 8.71 (d, $J = 8.7$ Hz, 1H), 8.01 (d, $J = 1.2$ Hz, 1H), 7.40-7.30 (m, 1H), 7.28 (dd, $J = 8.8, 1.4$ Hz, 2H), 7.18-7.14 (m, 4H), 7.87 (d, $J = 8.8$ Hz, 2H), 6.60-6.50 (br, 2H), 5.81 (s, 2H), 4.63 (s, 2H), 1.75 (s, 3H); $m/z = 573$ ($M + 1$).

EXAMPLE 261C

3-[1-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyrrolidin-3-yl]propanoic acid



Step A- Ethyl 4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine-5-carboxylate. A flask containing **I-A15** (1 g, 2.95 mmol), **I-30** (0.84 g, 3.54 mmol) and potassium bicarbonate (1.47 g, 14.74 mmol) in *t*-BuOH (15 mL) was stirred at 70 °C for 16 h. The resulting mixture was concentrated *in vacuo*. DCM and MeOH were added to the residue, and solids were removed by filtration. The filtrate was concentrated *in vacuo*, and the residue was re-crystallized from EtOAc : petroleum ether. m/z = 495 (M + 1).

Step B- 4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5H-pyrrolo[2,3-d]pyrimidin-6(7H)-one. In a flask containing ethyl 4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine-5-carboxylate (1.3 g, 2.63 mmol) in EtOH (50 mL) at 0 °C was added sodium hydroxide (6.6 mL, 13.2 mmol, 2 M) dropwise. The resulting mixture was stirred for 10 min at 0 °C before the reaction was quenched by the addition of aq. sat. NH_4Cl and extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography with EtOAc : petroleum ether to afford the title compound. m/z = 423 (M + 1).

Step C- Ethyl 3-(1-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}pyrrolidin-3-yl)propanoate. To a flask containing 4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5H-pyrrolo[2,3-d]pyrimidin-6(7H)-one (300 mg, 0.71 mmol) in DCM (10 mL) was added bromine (227 mg, 1.42 mmol). The mixture was stirred at RT for 3 h before ethyl 3-(pyrrolidin-3-yl)propanoate (1460 mg, 8.51 mmol) was added. The resulting mixture was stirred for 2 h at RT, then quenched by the addition of water, and extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with MeOH:DCM (0-10%) to afford the racemic title compound. The racemic material was resolved using Chiral HPLC

(CHIRALPAK IA) to afford 4 peaks, isomer **A** (faster eluting), isomer **B** (second eluting), isomer **C** (third eluting), and isomer **D** (slower eluting). $m/z = 592$ ($M + 1$).

Step D- 3-(1-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-

dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyrrolidin-3-yl)propanoic acid. A flask containing

ethyl 3-(1-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-

dihydro-5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyrrolidin-3-yl)propanoate isomer **C** (47 mg, 0.079

mmol), and lithium hydroxide (2 mL, 2 M in water) in THF (6 mL) was stirred for 16 h at RT.

The mixture was concentrated *in vacuo*, water (3 mL) and hydrogen chloride (2 mL, 2 M in

water) were added to the residue. Solids were collected by filtration and washed with water (3X)

and dried to afford the title product **Ex-261C**. ^1H NMR (400 MHz, CD_3OD) δ 8.64 (d, $J = 8.8$ Hz,

1H), 7.71 (s, 1H), 7.36-7.27 (m, 2H), 7.17-7.08 (m, 3H), 5.79 (s, 2H), 3.48-3.30 (m, 1H), 3.27-

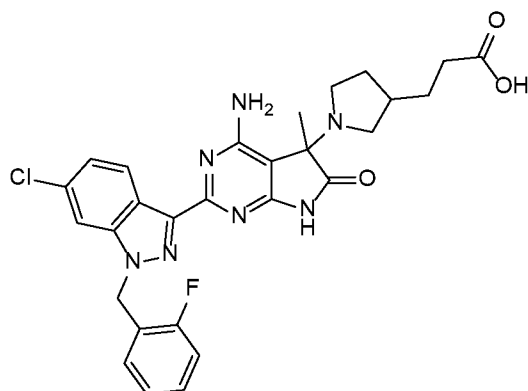
2.98 (m, 3H), 2.33-2.21 (m, 3H), 2.17-2.08 (m, 1H), 1.82 (s, 3H), 1.77-1.64 (m, 2H), 1.58-1.53

(m, 1H); $m/z = 564$ ($M + 1$).

EXAMPLE 261D

3-[1-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-

5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyrrolidin-3-yl]propanoic acid



Example **261D** was prepared using the same procedure as **Ex-261C** using ethyl 3-(1-{4-amino-2-

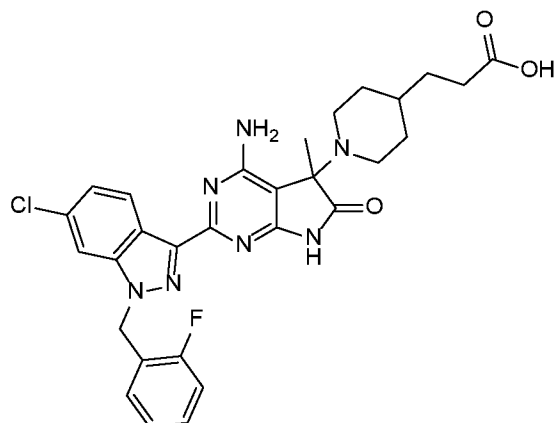
[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-

d]pyrimidin-5-yl}pyrrolidin-3-yl)propanoate isomer **D** as intermediate. $m/z = 564$ ($M + 1$).

EXAMPLE 262B

3-(1-{4-Amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-

5H-pyrrolo[2,3-*d*]pyrimidin-5-yl}piperidin-4-yl)propanoic acid

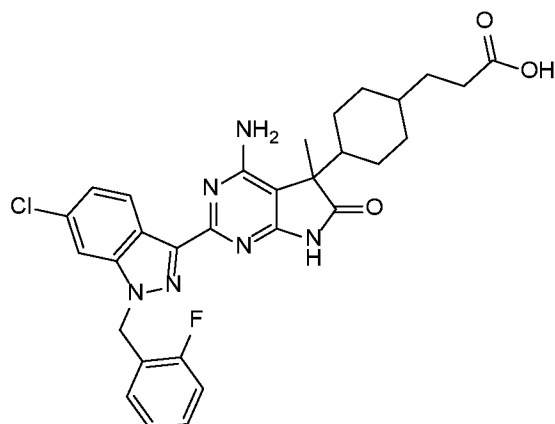


Ex-262B was prepared using the same protocol as **Ex-261C**, coupling 4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5H-pyrrolo[2,3-d]pyrimidin-6(7H)-one with ethyl 3-(piperidin-4-yl)propanoate to afford racemic ethyl 3-(4-{4-amino-2-[6-chloro-1-(2-

- 5 fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)cyclohexyl)propanoate which was resolved using Chiral HPLC (CHIRALPAK IC) to afford isomer **A** (faster eluting), and isomer **B** (slower eluting). Isomer **B** was used to prepare **Ex-262B**, $m/z = 578$ (M+1)

EXAMPLE 263AA

- 10 **3-(4-{4-Amino-2-[6-chloro-1-(3-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}cyclohexyl)propanoic acid**



- Step A- 4-Amino-5-(4-{[(*tert*-butyldimethylsilyl)oxy]methyl}cyclohexyl)-2-[6-chloro-1-(3-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5H-pyrrolo[2,3-d]pyrimidin-6(7H)-one.** A flask containing **I-A27** (0.8 g, 2.64 mmol), **I-68** (1 g, 2.64 mmol) and potassium bicarbonate (0.4 g, 3.96 mmol) in *t*-BuOH (20 mL) was stirred for 16 h at 70 °C. The reaction was quenched by the addition of water 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 purified by silica gel column chromatography with MeOH:DCM (0-10%) to afford the title compound. $m/z = 649$ ($M + 1$).

Step B- 4-Amino-2-[6-chloro-1-(3-fluorobenzyl)-1H-indazol-3-yl]-5-[4-

(hydroxymethyl)cyclohexyl]-5-methyl-5H-pyrrolo[2,3-d]pyrimidin-6(7H)-one. A flask

5 containing 4-amino-5-(4-{{(tert-butyl)dimethylsilyl}oxy}methyl}cyclohexyl)-2-[6-chloro-1-(3-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-5H-pyrrolo[2,3-d]pyrimidin-6(7H)-one (0.61 g, 0.940 mmol), *tetra-n*-butylammonium fluoride (1.3 g, 4.97 mmol) in THF (20 mL) was stirred for 16 h at RT. The reaction was quenched by the addition of brine and extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over anhydr. Na_2SO_4 , and filtered. The
10 filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc: petroleum ether (60-100%) to afford the title compound. $m/z = 535$ ($M + 1$).

Step C- 4-(4-Amino-2-(6-chloro-1-(3-fluorobenzyl)-1H-indazol-3-yl)-5-methyl-6-oxo-6,7-

dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)cyclohexanecarbaldehyde. To a flask under a inert

15 atmosphere of nitrogen, containing DMSO (0.14 mL, 1.97 mmol) and DCM (20 mL) at -78°C was added dropwise oxalyl chloride (0.14 mL, 1.65 mmol) in DCM (2 mL). The resulting mixture was stirred at -78°C for 30 min, before a solution of 4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1H-indazol-3-yl]-5-[4-(hydroxymethyl)cyclohexyl]-5-methyl-5H-pyrrolo[2,3-
20 *d*]pyrimidin-6(7H)-one (440 mg, 0.82 mmol) in DCM (2 mL) and DMSO (0.5 mL) was added dropwise at -78°C . The resulting mixture was stirred for 2 h at -78°C , then a solution of triethylamine (0.57 mL, 4.11 mmol) in DCM (2 mL) was added. The resulting mixture was stirred for 30 min at -78°C , then warmed to RT over 30 min. The reaction was quenched by the addition of water and extracted with DCM (3X). The organic layers were combined, washed with brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo*. The
25 residue was purified by silica gel column chromatography with EtOAc: petroleum ether (60-100%) to afford the title compound. $m/z = 533$ ($M + 1$).

Step D- Ethyl 3-(4-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1H-indazol-3-yl]-5-methyl-6-

oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl}cyclohexyl)acrylate. To a flask containing

ethyl 2-(diethoxyphosphoryl)acetate (1.75 g, 7.81 mmol) in Et_2O (40 mL) at 0°C was added

30 sodium hydride (311 mg, 7.79 mmol). The resulting mixture was stirred for 15 min at RT before a solution of 4-(4-amino-2-(6-chloro-1-(3-fluorobenzyl)-1H-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-5-yl)cyclohexanecarbaldehyde (415 mg, 0.779 mmol) in THF (6 mL) was added. The resulting mixture was stirred for 2 h at RT before it was quenched

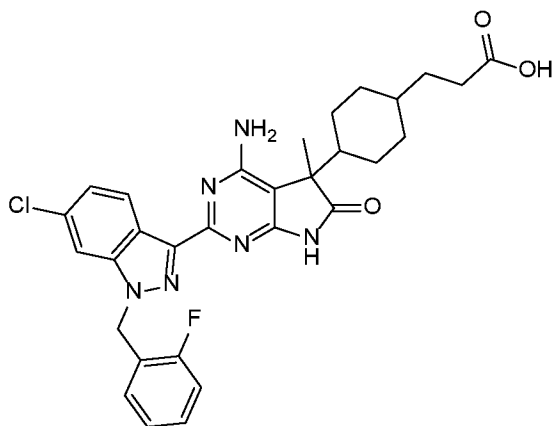
by the addition of aq. sat. NH_4Cl , extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. Na_2SO_4 , and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA modifier) to afford the title compound. $m/z = 603$ ($M + 1$).

- 5 **Step E- Ethyl 3-(4-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}cyclohexyl)propanoate.** A flask containing ethyl 3-(4-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}cyclohexyl)acrylate (370 mg, 0.61 mmol), 4-methylbenzenesulfonylhydrazide (472 mg, 2.53 mmol), sodium acetate (347 mg, 4.23 mmol) in
10 diethylene glycol dimethyl ether (10 mL) and water (1 mL) was stirred at 80 °C for 16 h. The reaction was quenched by the addition of water, extracted with EtOAc (3X). The organic layer was washed with brine, dried over anhydr. Na_2SO_4 , filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography with EtOAc: petroleum ether (0-10%). The residue was purified by reverse phase HPLC (ACN/water with 0.05% TFA
15 modifier). to afford isomer **A** (faster eluting), and isomer **B** (slower eluting). The racemic isomer **A** was resolved using chiral SFC (CHIRALPAK IC) to afford isomer **AA** (faster eluting), isomer **AB** (slower eluting). $m/z = 605$ ($M + 1$).

- Step F- 3-(4-{4-Amino-2-[6-chloro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}cyclohexyl)propanoic acid.** A flask containing
20 ethyl 3-(4-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}cyclohexyl)propanoate isomer **AA** (34 mg, 0.056 mmol), lithium hydroxide hydrate (34 mg, 0.81 mmol) in a THF (4 mL): water (3 mL) mixture was stirred at RT for 16 h. The reaction was quenched by the addition of hydrochloric acid (8.1 mL, 0.1 N) extracted with EtOAc (3X). The organic layer was washed with brine, dried over
25 anhydr. Na_2SO_4 , filtered, and the filtrate was concentrated *in vacuo* to afford the title compound **Ex-263AA**. ^1H NMR (400 MHz, CD_3OD) δ 8.46 (d, $J = 8.4$ Hz, 1H), 7.86 (s, 1H), 7.40-7.37 (m, 2H), 7.19-7.02 (m, 3H), 5.87 (s, 2H), 2.27 (t, $J = 6.8$ Hz, 2H), 2.07-1.84 (m, 3H), 1.76-1.59 (m, 6H), 1.49-1.47 (m, 2H), 1.26-0.89 (m, 4H); $m/z = 577$ ($M + 1$).

EXAMPLE 263BA

- 30 **3-(4-{4-Amino-2-[6-chloro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}cyclohexyl)propanoic acid**



Ethyl 3-(4-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}cyclohexyl)propanoate isomer **B** prepared as in **Ex-263AA** was resolved using chiral SFC (CHIRALPAK IB) to afford isomer **BA** (faster eluting) and isomer **BB** (slower eluting). Ethyl 3-(4-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}cyclohexyl)propanoate **BA** was hydrolysed to afford the title compound **Ex -263BA**.

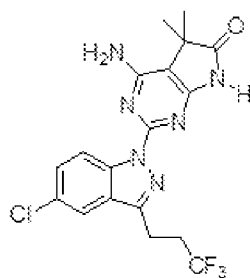
BIOLOGICAL ASSAYS:

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

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 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. CHO-K1 cells were transfected with plasmids pIREShygGCa1 and pIRESneo-hsGC $\beta 1$ simultaneously using FUGENE reagent. Clones that stably express both subunits were selected with hygromycin and neomycin for ~2 weeks. Clone #7 was chosen for the assay and was designated CHO-K1/sGC. CHO-K1/sGC cells were maintained in F-K12 medium containing 10% heat-inactivated Fetal Bovine Serum (FBS), 100 $\mu\text{g/mL}$ penicillin/streptomycin, 0.5 mg/mL hygromycin and 0.25 mg/mL G418. The cells were then cryopreserved in LN2. 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) (EAB) 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 are subsequently added and incubated for 1hr 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). The test compounds' activity 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 1500 nM. Data for the compounds of the Examples is provided in **Table 22**.

Table 22

EX.	IP (nM)	% Activation		EX.	IP (nM)	% Activation
1A	409	120		64B	302	101
2A	1058	111		65B	1101	136
3A	183	126		66B	238	107
4B	294	126		67B	384	115
5BA	132	76		68B	568	109

5BB	330	107		69B	289	139
6A	1263	85		70B	649	120
7A	1026	98		71B	73	78
8B	1363	129		72A	42	80
9B	1371	118		73B	85	87
10B	456	117		74A	62	94
11B	537	99		75A	238	155
12B	2877	81		76B	99	101
13B	152	86		77B	489	105
14B	525	90		78A	1741	93
15B	1315	95		79B	843	124
16B	1473	96		80A	733	98
17AB	3781	77		81B	504	110
18B	2497	95		82B	1367	107
19B	1042	89		83B	1421	80
20B	2209	88		84A	130	113
21B	362	93		85A	700	130
22A	423	91		86A	247	102
23B	203	109		87B	547	97
24A	210	106		88B	1247	88
25B	201	147		89B	442	108
26B	1922	102		90B	129	112
27B	331	120		91B	132	123
28B	2173	105		92B	219	111
29B	686	82		93A	575	63
30B	176	93		94B	178	108
31B	8333	130		95B	157	118
32B	445	79		96B	311	54
33B	804	100		97B	1146	122
34AA	437	81		98A	254	83
34AB	771	115		99B	186	110

35B	2794	102		100B	1803	109
36B	916	105		101B	2338	111
37B	762	96		102B	573	100
38B	220	98		103B	2946	104
39B	1091	82		104B	1372	106
40B	2561	94		105B	2159	97
41B	779	85		106B	1499	70
42B	1052	84		107B	397	113
43B	142	105		108B	842	122
44B	245	127		109B	1663	78
45B	210	95		110B	1127	78
46B	647	95		111B	9254	86
47B	218	88		112B	2516	130
48A	257	102		113B	568	89
49A	119	91		114A	1340	108
50A	407	98		115A	122	79
51B	485	116		116A	608	78
52B	504	109		117A	302	69
53A	124	102		118A	3510	86
54A	490	106		119B	839	103
55A	432	105		120B	1933	127
56A	134	116		121B	238	118
57B	1083	104		122B	895	115
58B	1130	65		123AA	880	79.0
59B	858	116		123AB	1957	95.8
60B	167	128		124AA	1600	76.5
61A	299	109		125AB	56	138.4
62A	141	148		126AA	74	89.0
63A	104	72		126AB	199	109.2
127A	52	117.1		194A	73	128.3
128A	137	116.8		195A	194	103.1

129A	51	98.5	196A	54	90.3
130A	1228	115.7	197B	125	106.2
131B	1061	119.9	198B	1071	134.2
132AA	125	108.6	199A	66	108.5
132AB	89	109.2	200A	220	120.4
133AA	657	103.8	201A	39	91.2
133AB	714	111.4	202A	212	122.5
134AA	807	103.5	203A	330	122.2
135A	254	92.9	204A	47	97.8
136AA	11	78.2	206B	549	113.4
136AB	23	71.4	207B	1761	100.1
137AA	121	92.1	208A	453	101.4
137AB	38	98.4	209B	2475	94.4
138B	375	114.5	210B	2019	103.0
139B	3455	134.8	211A	1176	96.2
140A	798	99.0	212A	119	134.9
141A	193	98.7	213A	839	94.9
142B	264	108.8	214A	320	116.1
143B	3379	76.1	215A	3701	118.8
144A	1219	93.1	216A	678	132.2
145A	391	82.9	217A	1424	123.6
146A	94	82.1	218A	301	102.8
147A	61	73.4	220B	82	112.8
148A	238	87.8	221B	150	92.1
149A	111	103.3	222A	71	104.7
150A	294	102.2	223A	210	118.8
151A	194	130.6	224A	14	111.3
152A	120	118.1	225B	460	139.8
153A	145	118.9	226A	355	112.5
154A	577	103.9	227B	74	63.5
156A	161	93.5	228A	64	95.0

157A	185	143.4	229AA	770	114.6
158A	353	88.8	229AB	179	72.9
159A	221	112.7	230AA	821	99.1
160B	111	107.8	231AA	113	148.2
161A	291	120.9	231AB	529	127.9
162A	69	76.5	232B	4154	89.1
163B	408	90.8	233A	204	141.1
164A	439	127.2	234B	265	135.2
165A	48	110.1	235B	626	86.8
166A	40	86.4	236A	478	109.8
167B	93	107.3	237B	5871	93.3
168B	207	141.2	238A	609	99.5
169B	159	90.3	239A	350	62.3
170B	655	129.9	240B	749	104.0
171A	1218	135.1	241A	403	94.8
172A	1034	92.7	242B	3097	107.3
173A	557	83.4	243A	3601	101.1
174A	682	120.9	244A	2726	93.3
175A	96	139.1	246A	7124	95.3
176B	1465	117.9	247A	4018	86.9
177B	351	125.7	248B	116	106.1
178A	429	123.8	249B	2618	98.5
179A	262	117.8	250B	1704	102.5
180A	228	121.4	252B	2460	87.6
181A	278	111.9	253A	3629	96.7
182A	238	92.0	254A	1013	123.3
183A	88	111.3	255A	1481	108.4
184A	230	97.7	256B	2048	104.4
185A	426	109.5	257A	106	84.7
186A	205	83.3	258B	1732	98.2
187A	244	97.1	259B	560	116.2

188A	109	123.7	260A	125	135.6
189A	51	115.6	261C	293	112.9
190A	49	119.6	261D	444	103.8
191B	133	113.7	262B	27	82.4
192A	1042	102.8	263AA	110	82.1
193B	69	89.2			

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] **Ex-77B** as the radioligand.

5 [³H] **Ex-77B** was prepared using a standardized tritium exchange procedure. The parent (non-labeled) molecule was first iodinated then a Pd-catalyzed iodine to tritium exchange provided the labeled compound.

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.

10 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] **Ex-77B** for 24 hours 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 μM of **Ex-77B**. After the incubation period, the binding mixtures were loaded onto the

15 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 μl of UltimaGold scintillation cocktail. The sealed plates were shaken vigorously and span, and counted after 6 hours with a Wallac Microbeta TriLux 1450 LSC & Luminescence Counter (Perkin Elmer). Data

20 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 1 nM. Data for the compounds of the Examples is provided in **Table 23**.

Table 23

EXAMPLE	K _i (pM)		EXAMPLE	K _i (pM)
1A	47		61A	66

2A	322		62A	22
3A	67		64B	75
4B	391		66B	495
5BA	162		67B	154
5BB	182		68B	3100
6A	130		69B	101
7A	154		76B	87
9B	374		77B	232
10B	150		78A	944
11B	304		79B	420
12B	2045		80A	755
13B	112		82B	223
14B	210		83B	1737
15B	455		84A	166
16B	1135		85A	1497
17AB	936		86A	323
18B	920		87B	785
19B	286		88B	848
20B	4491		89B	343
21B	64		90B	63
22A	78		91B	180
23B	99		92B	175
25B	262		93A	602
26B	266		95B	60
27B	221		96B	12150
28B	536		97B	799
29B	564		98A	395
30B	560		100B	39
31B	1412		101B	26

32B	1700		103B	45
33B	594		105B	42
34AA	138		106B	58
34AB	231		108B	56
35B	1119		109B	1998
36B	908		110B	361
37B	484		111B	1113
38B	145		112B	66
39B	3652		113B	64
40B	4379		114A	92
41B	717		116A	296
42B	951		118A	166
43B	96		119B	292
44B	123		120B	410
45B	182		121B	234
46B	216		122B	326
47B	114		123AA	1231
52B	413		123AB	874
57B	96		124AA	506
58B	493		124AB	617
59B	293		125AA	783
60B	102		125AB	336
126AA	100		194A	41
126AB	77		195A	92
127A	57		196A	468
128A	111		197B	162
129A	117		198B	107
130A	184		199A	70
131B	125		200A	52

132AA	105		201A	151
132AB	74		202A	186
133AA	513		203A	71
133AB	359		204A	269
134AA	320		206B	798
134AB	461		207B	95
135A	275		208A	253
136AA	252		209B	1642
136AB	218		210B	341
137AA	128		211A	258
137AB	204		212A	72
138B	58		213A	123
139B	114		214A	267
140A	227		215A	189
141A	665		216A	110
142B	183		217A	67
143B	174		218A	57
144A	594		219A	183
145A	299		220B	87
146A	62		221B	163
147A	75		222A	112
148A	123		223A	50
149A	167		224A	67
150A	96		225B	342
151A	124		226A	176
152A	31		227B	146
153A	118		228A	79
154A	91		229AA	496
155B	420		229AB	238

156A	170		230AA	185
157A	258		230AB	280
158A	864		231AA	92
159A	125		231AB	87
160B	62		232B	85
161A	81		233A	83
162A	150		234B	947
163B	1852		235B	404
164A	99		236A	158
165A	81		237B	193
166A	144		238A	95
167B	70		239A	68
168B	164		240B	75
169B	104		241A	121
170B	118		242B	1111
171A	94		243A	62
172A	98		244A	63
173A	252		245B	333
174A	173		246A	220
175A	151		247A	242
176B	130		248B	48
177B	118		249B	68
178A	116		250B	108
179A	144		251B	182
180A	31		252B	292
181A	94		253A	146
182A	124		254A	199
183A	76		255A	73
184A	92		256B	74

185A	165		257A	105
186A	120		258B	80
187A	29		259B	111
188A	100		260A	58
189A	49		261C	74
190A	31		261D	187
191B	109		262B	97
192A	116		263AA	235
193B	52		263BA	127

Acute Efficacy in spontaneously hypertensive rats (SHR)

Spontaneously hypertensive rats (SHR, male, Charles River) were implanted with DSI TA11PA-C40 telemetry device (Data Sciences, Inc., St. Paul, MN) under isoflurane or ketamine/metomidine anesthesia. The telemetry unit catheter was inserted into the descending aorta via the femoral artery and the telemetry device was implanted subcutaneously in the left flank area. Animals were allowed to recover from surgery for 14 days before the start of any studies. Blood pressure, heart rate, and activity signals from conscious, freely moving rats were recorded continuously for 30 seconds every 10 minutes. On the day prior to administration of compound, a single oral dose of vehicle (10% transcutol/20% Cremophor/70% water) was administered to all animals to establish baseline control data. The blood pressure lowering efficacy of compound (PO) or vehicle was evaluated following a single oral gavage. Data were collected as hourly averages, and changes in blood pressure were calculated by subtracting control baseline data on an hourly basis. Animals were maintained on normal diet with a 12 hour light-dark cycle.

Maximum peak decreases of systolic blood pressure (SBP) in SHR at a particular P.O. dose (mpk milligrams per kilogram) for the following Example compounds are provided.

Category A= decrease in SBP in SHRs 5-25 mmHg;

Category B= decrease in SBP in SHRs 25-40 mmHg;

Category C= decrease in SBP in SHRs >40 mmHg.

Table 24

EXAMPLE	Dose (P.O. mpk)	Category
2A	3	A
5BA	3	B
7A	3	A

9B	3	A
10B	3	A
13B	3	A
14B	3	A
21B	3	A
22A	3	A
27B	1	A
33B	3	B
34AA	3	A
34AB	1	A
38B	3	A
44B	3	C
45B	3	B
46B	3	A
52B	3	A
58B	3	A
59B	3	A
70B	3	A
76B	3	B
77B	1	C
79B	3	A
82B	3	A
84A	1	C
86A	1	A
89B	3	B
90B	1	B
92B	0.3	A
121B	3	A

Acute efficacy in hypoxia-induced pulmonary hypertension in rat following intratracheal administration

Charles River Sprague-Dawley (CD) male rats weighing approximately 350 g were
5 implanted with HD-S21 dual pressure telemetry transmitters (Data Sciences International (DSI))
into the pulmonary artery and femoral artery. This transmitter enables simultaneous
measurement of both pulmonary and systemic hemodynamic parameters in the same animal.
After a 7-10 day post-operative recovery period, animals were subjected to a normobaric

hypoxic (10% oxygen) environment using a Higher Peak Mountain Air Generator (MAG-10) connected to a modified rodent cage via a fitted inlet port. Oxygen (at 10%), temperature, humidity, and CO₂ were controlled within normal range and animals were maintained on a 12 hour light-dark cycle with ad libitum access to food and water. After two weeks exposure to 10% O₂ hypoxic environment, systolic pulmonary arterial pressure readings increased from ~25 mmHg to greater than 50 mmHg. Using a 48 hour baseline average, animals with readings between 50-110 mmHg (standard deviation of less than 10 mmHg) and minimal changes in systolic systemic blood pressure were enrolled for study. Animals were utilized for up to 2 studies per week for 4 weeks with a minimum of 2 days washout between doses of test agent.

Compound or vehicle was administered intra-tracheally under light isoflurane anesthesia (5% in oxygen; flow rate 2.0 L/min for 3 minutes). Once anesthetized, rats were placed on an angled intubation stand in supine position and the trachea visualized using a small laryngoscope. Animals then received either 0.5 mL/kg of vehicle or 0.5 mL/kg vehicle containing compound intra-tracheally delivered via microsyringer by use of a Penn-Century Microsprayer® needle 3” (Model IA-1B-GP) attached to a 1 mL high pressure syringe (Penn Century-Model B-SYR-PL1000) (Penn-Century, Philadelphia, PA). The Microsprayer® tip was inserted into the trachea up to the point at which the bend in the needle is close to the tip of the snout, which positions the tip of the Microsprayer® in front of the carina (bifurcation of trachea at the bronchi). After dose delivery the animal is placed on its back in the home cage for recovery.

Hemodynamic measurements were continuously recorded and readings consolidated to hourly moving averages. Each animal received a vehicle on Day 1 followed by vehicle or test agent on Day 2. Change from vehicle baseline was calculated by subtracting the hourly Day 1 vehicle response from the hourly Day 2 response and treatment group data was expressed as mean ± SEM.

Decreases of systolic blood pressure (SBP) and systolic pulmonary arterial pressure (PAP) were measured at a particular IT dose (mpk milligrams per kilogram) for the following Example compounds. Compounds in the **Table 25** achieved a minimum decrease in PAP of ≥15 mmHg for the corresponding decrease in SBP listed.

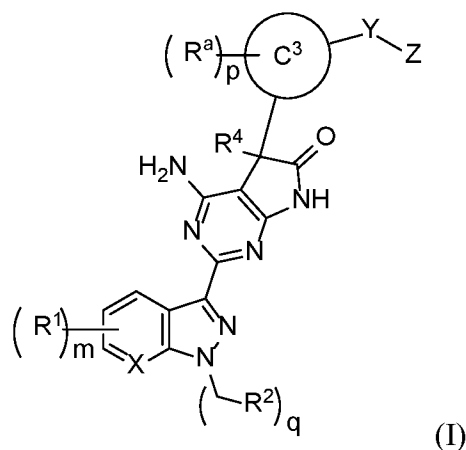
Category A= decrease in SBP 0-5 mmHg;
Category B= decrease in SBP 5-10 mmHg;
Category C= decrease in SBP >10 mmHg.

Table 25

EXAMPLE	Dose (IT mpk)	Category
2A	0.03 mpk	A
3A	0.01 mpk	A
7A	0.1 mpk	B
10B	0.01 mpk	A
11B	0.03 mpk	B
12B	0.1 mpk	B
21B	0.03 mpk	A
46B	0.03 mpk	A
47B	0.03 mpk	A
51B	0.01 mpk	A
63A	0.01 mpk	A
77B	0.03 mpk	A
80BA	0.1 mpk	B
81B	0.03 mpk	B
84A	0.03 mpk	A
92B	0.03 mpk	A
95B	0.03 mpk	A
112B	0.01 mpk	A
119B	0.03 mpk	A
127A	0.03 mpk	A
160B	0.01 mpk	B
163B	0.03 mpk	C
185A	0.01 mpk	A
195A	0.01 mpk	B
202A	0.01 mpk	A
220B	0.01 mpk	B
222A	0.01 mpk	B
235B	0.01 mpk	A
239A	0.01 mpk	A

CLAIMS

1. A compound of the Formula (I)



or a pharmaceutically acceptable salt thereof, wherein:

X is C(H) or N;

each R¹ is independently halo, hydroxy, C₁-C₃ alkyl, C₃-C₆ cycloalkyl or -O-C₁-C₃ alkyl;

R² is:

- (a.) C₁-C₆ alkyl, wherein said C₁-C₆ alkyl of R² is unsubstituted or substituted by 1 to 6 moieties independently selected from fluoro or -O-C₁-C₃ alkyl;
- (b.) ring C², wherein ring C² is:
 - (i.) C₃-C₁₂ cycloalkyl;
 - (ii.) phenyl;
 - (iii.) a 5- or 6-membered monocyclic heteroaryl containing 1 to 2 heteroatoms selected from N, O, or S; or
 - (iv.) a 5- or 6-membered monocyclic heterocyclyl containing 1 to 2 heteroatoms selected from N, O, or S;

wherein ring C² is unsubstituted or substituted by 1 to 3 moieties independently selected from halo, cyano, C₁-C₃ alkyl, -O-C₁-C₃ alkyl, or oxo;

R⁴ is C₁-C₆ alkyl, CF₃, or C₃-C₆ cycloalkyl;

ring C³ is:

- (a.) phenyl;
- (b.) a 5- or 6-membered monocyclic heteroaryl or a 9- to 10-membered bicyclic heteroaryl containing 1 to 3 heteroatoms selected from N, O, or S;

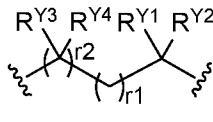
(c.) a 5- or 6-membered monocyclic heterocyclyl containing 1 to 3 heteroatoms selected from N, O, or S; or

(d.) C₃-C₆ cycloalkyl;

each R^a is independently selected from halo, cyano, C₁-C₃ alkyl, -O-C₁-C₃ alkyl, oxo, or hydroxy;

Y is:

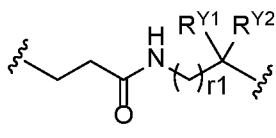
(a.) a bond;



(b.) a group of the formula

wherein RY₁ and RY₂ are independently H, C₁-C₃ alkyl, hydroxy, fluoro, C₁-C₃ hydroxyalkyl, or amino; or alternatively RY₁ and RY₂, together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl;

RY₃ and RY₄ are independently H, C₁-C₃ alkyl, hydroxy, fluoro, or C₁-C₃ hydroxyalkyl; or alternatively RY₃ and RY₄, together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl;



(c.) a group of the formula

(d.) ring A^H, wherein ring A^H is C₃-C₆ cycloalkyl or phenyl, wherein ring A^H is unsubstituted or substituted by 1 to 3 moieties independently selected from halo or C₁-C₃ alkyl;

(e.) a group -CH=CH-; or

(f.) a group ;

Z is:

(a.) -CO₂H; (b.) -C(O)N(H)OH; (c.) ; (d.) ; (e.) ;
 (f.) -SO₃H; (g.) -P(=O)(OH)₂; or (h.) -C(O)N(H)S(O)₂CH₃;

the subscript m is 0, 1, or 2;

the subscript p is 0, 1, 2, or 3;

the subscript q is 0 or 1;
 the subscript r1 is 0, 1, 2, 3, or 4; and
 the subscript r2 is 0 or 1.

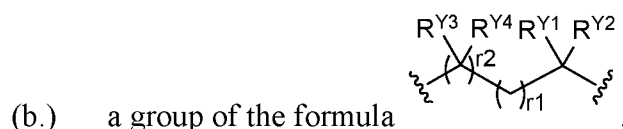
2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein:
 ring C³ is:

- (a.) phenyl;
- (b.) a 5- or 6-membered monocyclic heteroaryl containing 1 to 3 heteroatoms selected from N, O, or S;
- (c.) a 5- or 6-membered monocyclic heterocyclyl containing 1 to 3 heteroatoms selected from N, O, or S; or
- (d.) C₃-C₆ cycloalkyl;

each R^a is independently selected from halo, cyano, C₁-C₃ alkyl, -O-C₁-C₃ alkyl, or oxo;

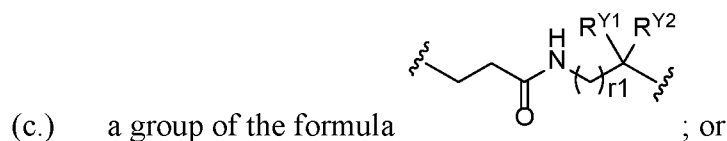
Y is:

- (a.) a bond;



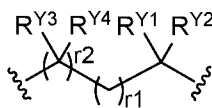
wherein R^{Y1} and R^{Y2} are independently H, C₁-C₃ alkyl, hydroxy, fluoro, or C₁-C₃ hydroxyalkyl; or alternatively R^{Y1} and R^{Y2}, together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl;

R^{Y3} and R^{Y4} are independently H, C₁-C₃ alkyl, hydroxy, fluoro, or C₁-C₃ hydroxyalkyl; or alternatively R^{Y3} and R^{Y4}, together with the carbon atom to which they are attached form a C₃-C₆ cycloalkyl;



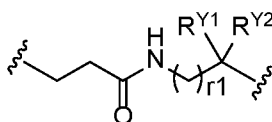
- (d.) ring A^H, wherein ring A^H is C₃-C₆ cycloalkyl or phenyl, wherein ring A^H is unsubstituted or substituted by 1 to 3 moieties independently selected from halo or C₁-C₃ alkyl.

3. The compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein the subscript q is 1, and R² is C₂-C₃ alkyl which is unsubstituted or substituted by 1 to 5 fluoro.
4. The compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein the subscript q is 1;
R² is ring C²;
ring C² is phenyl, cyclohexyl, adamantyl, pyridyl, or tetrahydropyranyl;
wherein ring C² is unsubstituted or independently substituted by 1 to 3 fluoro or methyl.
5. The compound of any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, wherein ring C³ is phenyl, thiazolyl, oxazolyl, oxadiazolyl, triazolyl, or pyridyl.
6. The compound of any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof,



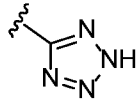
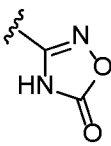
wherein Y is the group of the formula

7. The compound of any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof,

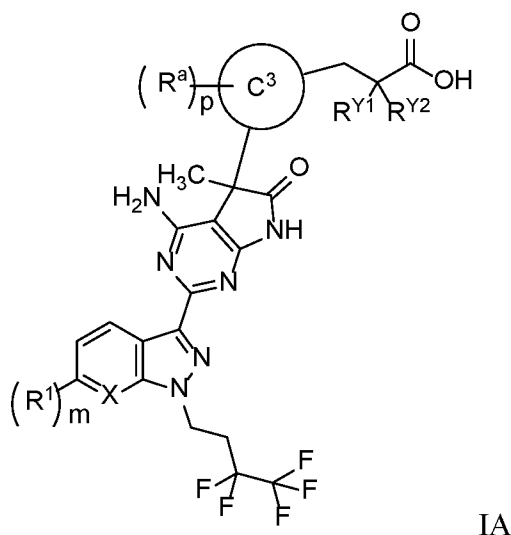


wherein Y is the group of the formula

8. The compound of claim 6 or a pharmaceutically acceptable salt thereof, wherein the subscript r1 is 1;
the subscript r2 is 0; and
R^{Y1} and R^{Y2} are independently H or C₁-C₃ alkyl.
9. The compound of any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof,

wherein Z is (a.) -CO₂H; (b.) -C(O)N(H)OH; (c.) ; or (d.) .

10. The compound of claim 9 or a pharmaceutically acceptable salt thereof, wherein Z is -CO₂H.
11. The compound of any one of claims 1 to 10, wherein X is C(H).
12. The compound of any one of claims 1 to 10, wherein X is N.
13. The compound of any one of claims 1 to 12, wherein R⁴ is methyl or cyclopropyl.
14. The compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) has the Formula (IA)



wherein

X is C(H) or N;

R¹ is methyl or halo;

C³ is phenyl or thiazolyl;

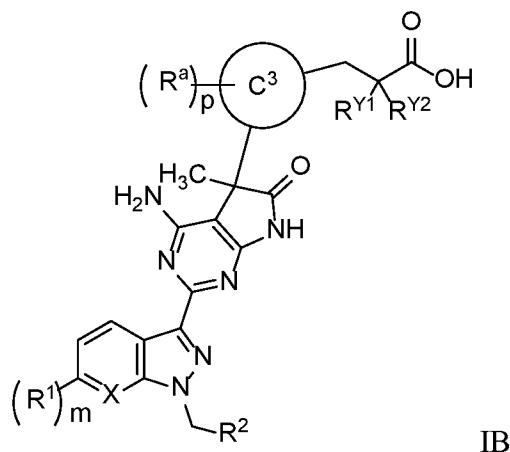
R^a is methyl, cyano, or halo;

R^{Y1} and R^{Y2} are independently H or methyl;

the subscript m is 0 or 1; and

the subscript p is 0 or 1.

15. The compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) has the Formula (IB)



wherein

X is C(H) or N;

R¹ is methyl or halo;

R² is ring C², wherein ring C² is:

- (i.) C₃-C₁₂ cycloalkyl;
- (ii.) phenyl;
- (iii.) a 5- or 6-membered monocyclic heteroaryl containing 1 to 2 heteroatoms selected from N, O, or S; or
- (iv.) a 5- or 6-membered monocyclic heterocyclyl containing 1 to 2 heteroatoms selected from N, O, or S;

wherein ring C² is unsubstituted or substituted by 1 to 3 moieties independently selected from halo, cyano, C₁-C₃ alkyl, -O-C₁-C₃ alkyl, or oxo

C³ is phenyl, thiazolyl, or oxazolyl;

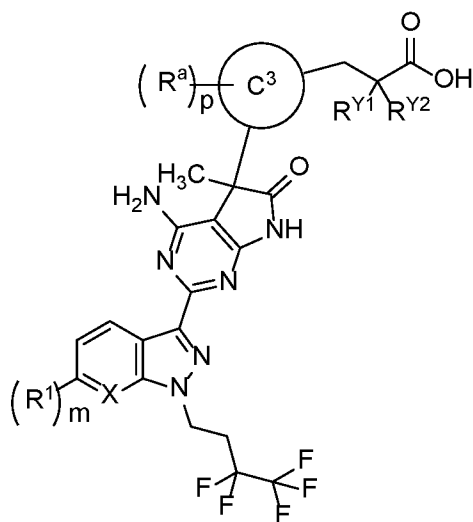
R^a is methyl, cyano, or halo;

R^{Y1} and R^{Y2} are independently H or methyl;

the subscript m is 0 or 1; and

the subscript p is 0 or 1.

16. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) has the Formula (IA)



IA

wherein

X is C(H) or N;

R¹ is halo;

C³ is phenyl, thiazolyl, oxazolyl, or benzothiazolyl;

R^a is methyl, cyano, or halo;

R^{Y1} and R^{Y2} are independently H, methyl, or amino;

the subscript m is 0 or 1; and

the subscript p is 0 or 1.

17. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is:

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

3-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-bromophenyl)propanoic acid;

3-{4-[4-amino-2-{6-chloro-1-[(4-methylcyclohexyl)methyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

3-{4-[4-amino-2-{6-chloro-1-[tetrahydro-2*H*-pyran-2-ylmethyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

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

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

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

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

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

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

3-(4-{4-amino-2-(1-butyl-6-chloro-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-2-(1-butyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-5-methyl-6-oxo-2-[1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

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

3-(4-{4-amino-5-methyl-6-oxo-2-[1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2-methylpropanoic acid;

3-(4-{4-amino-2-[5-fluoro-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-5-methyl-2-[6-methyl-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(3-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(3-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-2-[1-(2,3-difluoro-4-methylbenzyl)-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}benzoic acid;

3-(3-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)acetic acid;

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)propanoic acid;

2-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)-2-methylpropanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)-2,2-dimethylpropanoic acid;

1-[(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1*H*-1,2,3-triazol-1-yl)methyl]cyclopropanecarboxylic acid;

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2-methylpropanoic acid;

2-{4-[4-amino-2-(1-butyl-6-chloro-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1*H*-1,2,3-triazol-1-yl}acetic acid;

3-{4-[4-amino-2-(1-butyl-6-chloro-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1*H*-1,2,3-triazol-1-yl}propanoic acid;

3-{4-[4-amino-2-(1-butyl-6-chloro-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}-2,2-dimethylpropanoic acid;

3-{4-[4-amino-2-(1-butyl-6-chloro-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

3-(3-{4-amino-2-[6-chloro-1-(2-methoxyethyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(2-methoxyethyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(4,4,4-trifluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(4,4,4-trifluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

3-{4-[4-amino-2-(6-chloro-1-pentyl-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(cyclohexylmethyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-{4-[4-amino-2-(6-chloro-1-hexyl-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

3-(4-{4-amino-2-[6-fluoro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(3-{4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

4-(2-{4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}thiazol-4-yl)butanoic acid;

3-(2-{4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)propanoic acid;

2-(2-{4-amino-2-(6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)acetic acid;

3-(4-{4-amino-2-[6-chloro-1-(4,4-dimethylpentyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(3-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)propanoic acid;

4-(2-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}thiazol-4-yl)butanoic acid;

3-(2-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

3-(4-[4-amino-2-{6-chloro-1-[(3-fluoropyridin-2-yl)methyl]-1*H*-indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl)propanoic acid;

3-(4-[4-amino-2-{6-chloro-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-indazol-3-yl}-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl)propanoic acid;

3-(4-{4-amino-2-[1-(2-fluorobenzyl)-6-methyl-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(3-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(2-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(2,6-difluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(4-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(4-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(2-methylbenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{2-[1-(adamantan-1-yl)methyl]-6-chloro-1*H*-indazol-3-yl]-4-amino-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(4-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(2-{4-amino-2-[5-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

3-(4-{4-amino-2-[5-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(2-{4-amino-2-[5-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

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

3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid ;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)benzoic acid;

4-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-5-methyl-1,3-thiazol-4-yl)benzoic acid;

3-(2-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-5-cyclopropyl-2-[5-fluoro-1-(4,4,4-trifluorobutyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}thiazol-4-yl)-2,2-dimethylpropanoic acid;

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

[5-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl]acetic acid;

2-[5-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-oxo-1,3,4-oxadiazol-3(2*H*)-yl]-2-methylpropanoic acid;

(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)glycine;

2-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamido)-2-methylpropanoic acid;

(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)-*D*-alanine;

(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)-*L*-alanine;

(2*R*)-2-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamido)butanoic acid;

(2*S*)-2-(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamido)butanoic acid;

(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)-*D*-serine;

(3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoyl)-*D*-threonine;

N-((2*H*-tetrazol-5-yl)methyl)-3-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanamide;

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

3-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-5-hydroxy-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-{4-[4-amino-2-(1-butyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]phenyl}propanoic acid;

4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-5-{4-[2-(2*H*-tetrazol-5-yl)ethyl]phenyl}-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one;

4-(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)butanoic acid;

(4-{4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)acetic acid;

4-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)butanoic acid;

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

2-(4-{4-amino-2-[6-chloro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)acetic acid;

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

3-(6-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}pyridin-3-yl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-cyanophenyl)propanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-methylphenyl)propanoic acid; or

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-2-hydroxyphenyl)propanoic acid.

18. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is:

3-(2-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}oxazol-4-yl)-2,2-dimethylpropanoic acid;

3-(4-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)propanoic acid;

3-(3-{4-amino-2-[6-chloro-1-(3,3,4,4,4-pentafluorobutyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}phenyl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[6-fluoro-1-(2-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-thiazol-4-yl)-2,2-dimethylpropanoic acid;

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

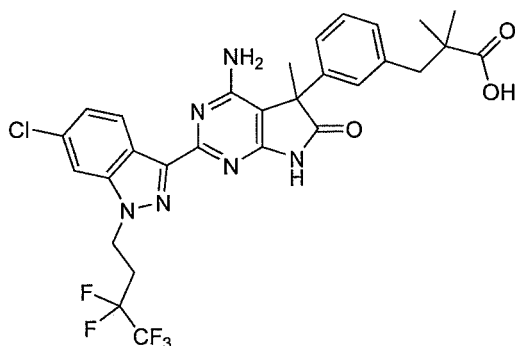
3-{2-[4-amino-2-{6-chloro-1-[(3-fluoropyridin-2-yl)methyl]-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]-1,3-oxazol-4-yl}-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[6-chloro-1-(3-fluorobenzyl)-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-5-methyl-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid;

3-(2-{4-amino-2-[1-(2,3-difluorobenzyl)-6-fluoro-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid; or

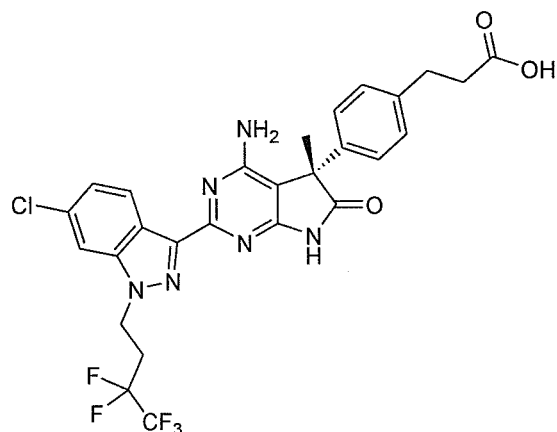
3-(2-{4-amino-2-[1-(cyclohexylmethyl)-6-fluoro-1*H*-indazol-3-yl]-5-methyl-6-oxo-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl}-1,3-oxazol-4-yl)-2,2-dimethylpropanoic acid.

19. The compound of claim 1, which is



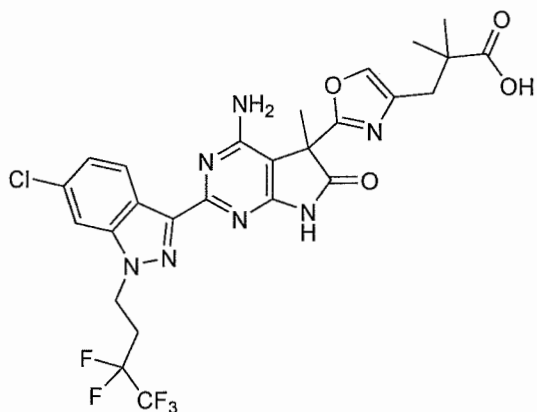
or a pharmaceutically acceptable salt thereof.

20. The compound of claim 1, which is



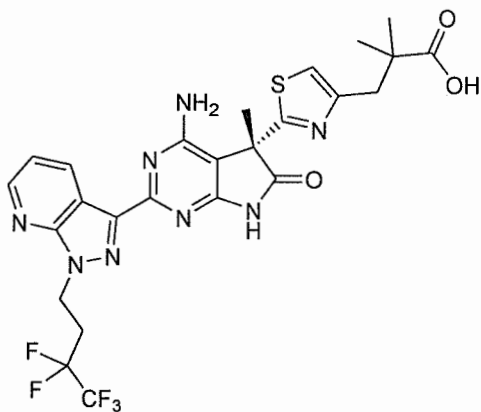
or a pharmaceutically acceptable salt thereof.

21. The compound of claim 1, which is



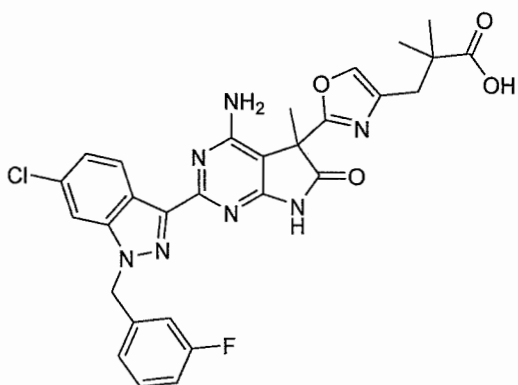
or a pharmaceutically acceptable salt thereof.

22. The compound of claim 1, which is



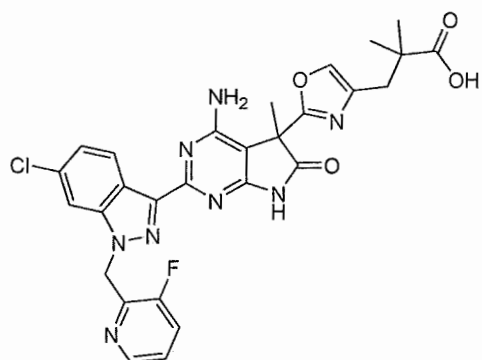
or a pharmaceutically acceptable salt thereof.

23. The compound of claim 1, which is



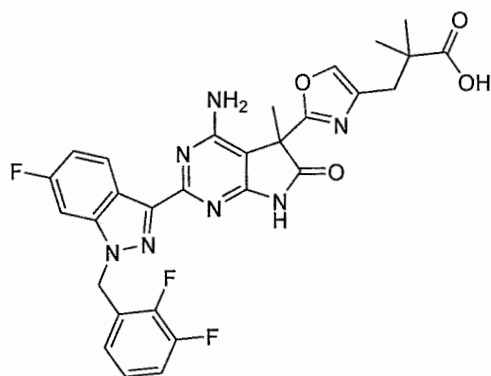
or a pharmaceutically acceptable salt thereof.

24. The compound of claim 1, which is



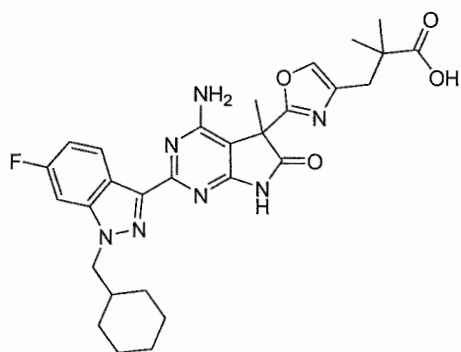
or a pharmaceutically acceptable salt thereof.

25. The compound of claim 1, which is



or a pharmaceutically acceptable salt thereof.

26. The compound of claim 1, which is



or a pharmaceutically salt thereof.

CC(C)(C)C[C@@H]1C(=O)Nc2c(N)nnc2C3=C(N1)C(=C4C(=CC(=CC=C4F)N3N5C6=CC=CC=C6F5)C7=CC=CC=C7F)S=C8N=CC=C8C8

or a pharmaceutically acceptable salt thereof.

28. A pharmaceutical composition comprising the compound of any one of claims 1 to 27 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

29. The pharmaceutical composition of claim 28, further comprising one or more additional active agents 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 or a metabolic altering agent.

30. The compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, for use in therapy.

31. The use of the compound of any one of claims 1 to 27, 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, acute respiratory distress syndrome (ARDS), chronic kidney disease, cystic fibrosis, sickle cell anemia, scleroderma, Raynaud's Syndrome, diabetes, diabetic retinopathy, cirrhosis of the liver, chronic obstructive pulmonary disease (COPD), acute lung injury, pulmonary fibrosis, or interstitial lung disease.

32. The use according to claim 31, wherein said condition is pulmonary hypertension.

33. The use according to claim 31, wherein said condition is heart failure.