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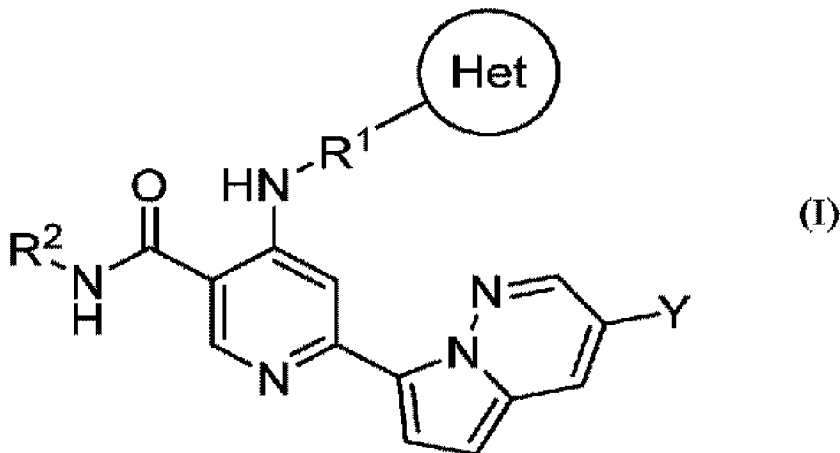
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(54) Title: PYRROLO[1,2-B]PYRIDAZINE DERIVATIVES AS IRAK4 INHIBITORS



(57) Abrégé/Abstract:

A compound of Formula (I) pharmaceutically acceptable salts thereof, deuterated analogs thereof, compositions thereof, and methods of treating disease using a compound thereof are disclosed.

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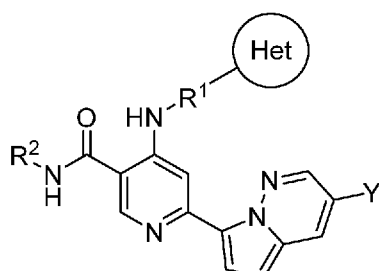
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(54) Title: PYRROLO[1,2-B]PYRIDAZINE DERIVATIVES AS IRAK4 INHIBITORS



(57) Abstract: A compound of Formula (I) pharmaceutically acceptable salts thereof, deuterated analogs thereof, compositions thereof, and methods of treating disease using a compound thereof are disclosed.



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## PYRROLO[1,2-B]PYRIDAZINE DERIVATIVES AS IRAK4 INHIBITORS

### FIELD

The present disclosure relates to novel compounds that are inhibitors of the kinase IRAK4. The disclosure also relates to methods for preparing the compounds and to  
5 pharmaceutical compositions comprising such compounds.

### BACKGROUND

Interleukin-1 receptor-associated kinase-4 (IRAK4) is a serine–threonine kinase which acts as a mediator in interleukin-1/Toll-like receptor (IL-1/TLR) signaling cascades. More particularly, IRAK4 is involved in activation of adaptor protein myeloid differentiation primary  
10 response gene 88 (MyD88) signaling cascades and is hypothesized to play a role in inflammatory and fibrotic disorders, such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), gout, Lyme disease, arthritis, psoriasis, pelvic inflammatory disease, systemic lupus erythematosus (SLE), Sjogren’s syndrome, viral myocarditis, acute and chronic tissue injury, non-alcoholic steatohepatitis (NASH), alcoholic hepatitis and kidney disease, including  
15 chronic kidney disease and diabetic kidney disease. In addition, IRAK4 plays a role in certain cancers and is hypothesized to play a role in inflammation associated with gastrointestinal infections, including *C. difficile*. Signaling through IL-1R/TLR results in the activation of MyD88 which recruits IRAK4 and IRAK1 to form a signaling complex. This complex then interacts with a series of kinases, adaptor proteins, and ligases, ultimately resulting in the  
20 activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B), activator protein-1 (AP1), cyclic AMP-responsive element-binding protein (CREB) and the interferon-regulatory factors (IRFs), including IRF5 and IRF7, inducing the generation of pro-inflammatory cytokines and type I interferons.

Therefore, inhibitors of IRAK4 may be useful in the treatment of inflammatory and  
25 fibrotic disorders, such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), gout, Lyme disease, arthritis, psoriasis, pelvic inflammatory disease, systemic lupus erythematosus (SLE), Sjogren’s syndrome, inflammation associated with gastrointestinal infections, including *C. difficile*, viral myocarditis, acute and chronic tissue injury, non-alcoholic steatohepatitis (NASH), alcoholic hepatitis and kidney disease, including chronic kidney disease and diabetic  
30 kidney disease. (Joosten, L.A.B et al., TOLL-LIKE RECEPTORS AND CHRONIC INFLAMMATION IN RHEUMATIC DISEASES: NEW DEVELOPMENTS, Nat. Rev. Rheumatol., 346 | JUNE 2016 12; 344-357 Published online 12 May 2016) (Valaperti, A. et al., INNATE IMMUNE INTERLEUKIN-1RECEPTOR-ASSOCIATED KINASE 4

EXACERBATES VIRAL MYOCARDITIS BY REDUCING CCR5<sup>+</sup>CD11b<sup>+</sup> MONOCYTE  
 MIGRATION AND IMPAIRING INTERFERON PRODUCTION, *Circulation*, **128** |  
 SEPTEMBER 2013 14; 1542-1554), as well as Type I interferonopathies, such as Aicardi-  
 Goutières syndrome, Familial chilblain lupus, and Retinal vasculopathy with cerebral  
 leukodystrophy, (**Lee-Kirsch et al.**, TYPE I INTERFERONOPATHIES—AN EXPANDING  
 5 DISEASE SPECTRUM OF IMMUNODYSREGULATION, *Semin. Immunopathol.* (2015)  
 37:349–357), (**Leaf, I.A. et al.**, PERICYTE MYD88 AND IRAK4 CONTROL  
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 10 **ENHANCES TGF- $\beta$  SIGNALING AND HEPATIC FIBROSIS**, *Nature Medicine*, **13** |  
 NOVEMBER 2007 11; 1324-1332), (**Garcia-Martinez, I. et al.**, HEPATOCYTE  
**MITOCHONDRIAL DNA DRIVES NONALCHOLIC STEATOHEPATITIS BY**  
**ACTIVATION OF TLR9**, *The Journal of Clinical Investigation*, **126** | MARCH 2016 3;  
 859-864).

15 In addition, certain cancers, including lymphomas, may contain one or more mutations in  
 the MYD88 adaptor protein, leading to a constitutively active signaling cascade that may  
 promote survival of tumor cells. (Kelly et al., IRAK4 inhibitors for autoimmunity and  
 lymphoma, *J. Exp. Med.* 2015 Vol. 212 No. 13 2189–2201)

Therefore, an inhibitor of IRAK4 may be useful in the treatment of cancers, including  
 20 lymphomas.

There are currently no approved IRAK4 inhibiting pharmaceuticals. Therefore, it would  
 be useful to provide an IRAK4 inhibiting compound with properties suitable for administration  
 as a pharmaceutical agent to a mammal, particularly a human. Considerations for selecting a  
 pharmaceutical compound are multifactorial. Compound characteristics including on-target  
 25 potency, pharmacokinetics, pKa, solubility, stability (e.g., metabolic stability) and off-target  
 liabilities are frequently profiled.

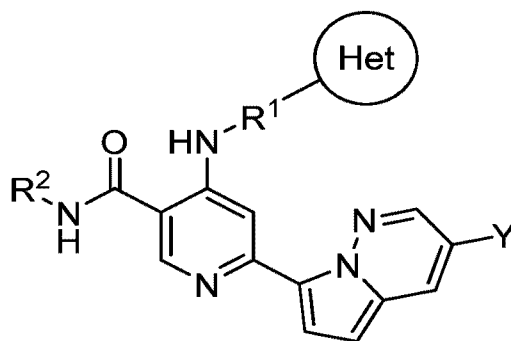
WO2016210034, WO2016210036, WO2015150995, WO2016127024, and  
 WO2016210037 recite compounds said to be useful as IRAK4 inhibitors.

### SUMMARY OF THE INVENTION

30 Provided herein are compounds and pharmaceutical compositions useful as inhibitors of  
 IRAK4. Some compounds of the disclosure may find use in pharmaceutical compositions,  
 together with at least one pharmaceutically acceptable excipient, for treating a subject in need  
 thereof. Compounds of the present disclosure also have been found to inhibit production of pro-

inflammatory cytokines TNF $\alpha$ , IL-6, IL-1 $\beta$ , IL-8, IL-12, IL-23 and type I interferons IFN $\alpha$  and IFN $\beta$ , all of which are mediators of inflammation and the immune response. The disclosure also provides compositions, including pharmaceutical compositions, kits that include the compounds, and methods of using and making the compounds.

5 In one embodiment of the disclosure, there is provided a compound of Formula (I):



(I)

wherein Y is selected from: -H, -F, -Cl, -Br, -CN, -CF<sub>3</sub>, -CF<sub>2</sub>H, -OH, and -OCH<sub>3</sub>;

R<sup>1</sup> is selected from C<sub>3-10</sub> cycloalkyl optionally substituted with X<sup>1</sup> and 4-12 membered  
10 heterocyclyl optionally substituted with X<sup>1</sup>;

wherein each X<sup>1</sup> is independently oxo, halo, -NO<sub>2</sub>, -N<sub>3</sub>, -CN, C<sub>1-9</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-15</sub> cycloalkyl, C<sub>1-8</sub> haloalkyl, -O-R<sup>12</sup>, -C(O)-R<sup>12</sup>, -C(O)O-R<sup>12</sup>, -C(O)-N(R<sup>12</sup>)(R<sup>12</sup>), -N(R<sup>12</sup>)(R<sup>12</sup>), -N(R<sup>12</sup>)<sub>2</sub>(R<sup>12</sup>)<sup>+</sup>, -N(R<sup>12</sup>)C(O)-R<sup>12</sup>, -N(R<sup>12</sup>)C(O)O-R<sup>12</sup>, or -N(R<sup>12</sup>)C(O)N(R<sup>12</sup>)(R<sup>12</sup>);

“Het” is selected from 5-10 membered heteroaryl optionally substituted with X<sup>2</sup> or 4-12  
15 membered heterocyclyl optionally substituted with X<sup>2</sup>;

wherein each X<sup>2</sup> is selected from oxo, halo, N<sub>3</sub>, -CN, C<sub>1-9</sub> alkyl, C<sub>3-6</sub> cycloalkyl C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-15</sub> cycloalkyl, C<sub>1-8</sub> haloalkyl, 4-12 membered heterocyclyl -O-R<sup>12</sup>, C<sub>1-6</sub> cyano alkyl, C<sub>1-6</sub> alkyl ether, -OC(O)R<sup>12</sup>, -OC(O)OR<sup>12</sup>, -OC(O)-N(R<sup>12</sup>)(R<sup>12</sup>), and -C(O)N(R<sup>12</sup>)(R<sup>12</sup>), wherein any alkyl, alkenyl, alkynyl, cycloalkyl, haloalkyl, or heterocyclyl is  
20 optionally substituted with Z<sup>1a</sup>;

R<sup>2</sup> is selected from:

- C<sub>1-10</sub> alkyl optionally substituted with Z<sup>1</sup>;
- C<sub>3-10</sub> cycloalkyl optionally substituted with Z<sup>1</sup>;
- 5-10 membered heteroaryl optionally substituted with Z<sup>1</sup>;
- 25 C<sub>6-10</sub> aryl optionally substituted with Z<sup>1</sup>; and

e) 4-12 membered heterocyclyl optionally substituted with Z<sup>1</sup>;

wherein Z<sup>1</sup> is independently oxo, halo, -NO<sub>2</sub>, -N<sub>3</sub>, -CN, C<sub>1-9</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-15</sub> cycloalkyl, C<sub>1-8</sub> haloalkyl, aryl, heteroaryl, heterocyclyl, -O-R<sup>12</sup>, -C(O)-R<sup>12</sup>, -C(O)O-R<sup>12</sup>, -C(O)-N(R<sup>12</sup>)(R<sup>12</sup>), -N(R<sup>12</sup>)(R<sup>12</sup>), -N(R<sup>12</sup>)<sub>2</sub>(R<sup>12</sup>)<sup>+</sup>, -N(R<sup>12</sup>)C(O)-R<sup>12</sup>, -N(R<sup>12</sup>)C(O)O-R<sup>12</sup>, -N(R<sup>12</sup>)C(O)N(R<sup>12</sup>)(R<sup>12</sup>), -N(R<sup>12</sup>)S(O)<sub>2</sub>(R<sup>12</sup>), -NR<sup>12</sup>S(O)<sub>2</sub>N(R<sup>12</sup>)(R<sup>12</sup>), -NR<sup>12</sup>S(O)<sub>2</sub>O(R<sup>12</sup>), -OC(O)R<sup>12</sup>, -OC(O)OR<sup>12</sup>, -OC(O)-N(R<sup>12</sup>)(R<sup>12</sup>), -Si(R<sup>12</sup>)<sub>3</sub>, -S-R<sup>12</sup>, -S(O)R<sup>12</sup>, -S(O)(NH)R<sup>12</sup>, -S(O)<sub>2</sub>R<sup>12</sup> or -S(O)<sub>2</sub>N(R<sup>12</sup>)(R<sup>12</sup>); wherein any alkyl, alkenyl, alkynyl, cycloalkyl, haloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with Z<sup>1a</sup>;

each Z<sup>1a</sup> is independently oxo, halo, -NO<sub>2</sub>, -CN, -N<sub>3</sub>, C<sub>1-9</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-15</sub> cycloalkyl, C<sub>1-8</sub> haloalkyl, aryl, heteroaryl, heterocyclyl, -O-R<sup>12</sup>, -C(O)R<sup>12</sup>, -C(O)O-R<sup>12</sup>, -C(O)N(R<sup>12</sup>)(R<sup>12</sup>), -N(R<sup>12</sup>)(R<sup>12</sup>), -N(R<sup>12</sup>)<sub>2</sub>(R<sup>12</sup>)<sup>+</sup>, -N(R<sup>12</sup>)-C(O)R<sup>12</sup>, -N(R<sup>12</sup>)C(O)O(R<sup>12</sup>), -N(R<sup>12</sup>)C(O)N(R<sup>12</sup>)(R<sup>12</sup>), -N(R<sup>12</sup>)S(O)<sub>2</sub>(R<sup>12</sup>), -N(R<sup>12</sup>)S(O)<sub>2</sub>-N(R<sup>12</sup>)(R<sup>12</sup>), -N(R<sup>12</sup>)S(O)<sub>2</sub>O(R<sup>12</sup>), -OC(O)R<sup>12</sup>, -OC(O)OR<sup>12</sup>, -OC(O)-N(R<sup>12</sup>)(R<sup>12</sup>), -Si(R<sup>12</sup>)<sub>3</sub>, -S-R<sup>12</sup>, -S(O)R<sup>12</sup>, -S(O)(NH)R<sup>12</sup>, -S(O)<sub>2</sub>R<sup>12</sup> or -S(O)<sub>2</sub>N(R<sup>12</sup>)(R<sup>12</sup>);

wherein any alkyl, alkenyl, alkynyl, cycloalkyl, haloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with Z<sup>1b</sup>;

each R<sup>12</sup> is independently H, C<sub>1-9</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-15</sub> cycloalkyl, aryl, heteroaryl or heterocyclyl;

wherein any alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with Z<sup>1a</sup>;

each Z<sup>1b</sup> is independently oxo, hydroxy, halo, -NO<sub>2</sub>, -N<sub>3</sub>, -CN, C<sub>1-9</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-15</sub> cycloalkyl, C<sub>1-8</sub> haloalkyl, aryl, heteroaryl, heterocyclyl, -O(C<sub>1-9</sub> alkyl), -O(C<sub>2-6</sub> alkenyl), -O(C<sub>2-6</sub> alkynyl), -O(C<sub>3-15</sub> cycloalkyl), -O(C<sub>1-8</sub> haloalkyl), -O(aryl), -O(heteroaryl), -O(heterocyclyl), -NH<sub>2</sub>, -NH(C<sub>1-9</sub> alkyl), -NH(C<sub>2-6</sub> alkenyl), -NH(C<sub>2-6</sub> alkynyl), -NH(C<sub>3-15</sub> cycloalkyl), -NH(C<sub>1-8</sub> haloalkyl), -NH(aryl), -NH(heteroaryl), -NH(heterocyclyl), -N(C<sub>1-9</sub> alkyl)<sub>2</sub>, -N(C<sub>3-15</sub> cycloalkyl)<sub>2</sub>, -N(C<sub>2-6</sub> alkenyl)<sub>2</sub>, -N(C<sub>2-6</sub> alkynyl)<sub>2</sub>, -N(C<sub>3-15</sub> cycloalkyl)<sub>2</sub>, -N(C<sub>1-8</sub> haloalkyl)<sub>2</sub>, -N(aryl)<sub>2</sub>, -N(heteroaryl)<sub>2</sub>, -N(heterocyclyl)<sub>2</sub>, -N(C<sub>1-9</sub> alkyl)(C<sub>3-15</sub> cycloalkyl), -N(C<sub>1-9</sub> alkyl)(C<sub>2-6</sub> alkenyl), -N(C<sub>1-9</sub> alkyl)(C<sub>2-6</sub> alkynyl), -N(C<sub>1-9</sub> alkyl)(C<sub>3-15</sub> cycloalkyl), -N(C<sub>1-9</sub> alkyl)(C<sub>1-8</sub> haloalkyl), -N(C<sub>1-9</sub> alkyl)(aryl), -N(C<sub>1-9</sub> alkyl)(heteroaryl), -N(C<sub>1-9</sub> alkyl)(heterocyclyl), -C(O)(C<sub>1-9</sub> alkyl), -C(O)(C<sub>2-6</sub> alkenyl), -C(O)(C<sub>2-6</sub> alkynyl), -C(O)(C<sub>3-15</sub> cycloalkyl), -C(O)(C<sub>1-8</sub> haloalkyl), -C(O)(aryl), -C(O)(heteroaryl), -C(O)(heterocyclyl), -C(O)O(C<sub>1-9</sub> alkyl), -C(O)O(C<sub>2-6</sub> alkenyl), -C(O)O(C<sub>2-6</sub> alkynyl), -C(O)O(C<sub>3-15</sub> cycloalkyl), -C(O)O(C<sub>1-8</sub> haloalkyl), -C(O)O(aryl), -C(O)O(heteroaryl), -C(O)O(heterocyclyl), -C(O)NH<sub>2</sub>, -

- C(O)NH(C<sub>1-9</sub> alkyl), -C(O)NH(C<sub>2-6</sub> alkenyl), -C(O)NH(C<sub>2-6</sub> alkynyl), -C(O)NH(C<sub>3-15</sub> cycloalkyl), -C(O)NH(C<sub>1-8</sub> haloalkyl), -C(O)NH(aryl), -C(O)NH(heteroaryl), -C(O)NH(heterocyclyl), -C(O)N(C<sub>1-9</sub> alkyl)<sub>2</sub>, -C(O)N(C<sub>3-15</sub> cycloalkyl)<sub>2</sub>, -C(O)N(C<sub>2-6</sub> alkenyl)<sub>2</sub>, -C(O)N(C<sub>2-6</sub> alkynyl)<sub>2</sub>, -C(O)N(C<sub>3-15</sub> cycloalkyl)<sub>2</sub>, -C(O)N(C<sub>1-8</sub> haloalkyl)<sub>2</sub>, -
- 5 C(O)N(aryl)<sub>2</sub>, -C(O)N(heteroaryl)<sub>2</sub>, -C(O)N(heterocyclyl)<sub>2</sub>, -NHC(O)(C<sub>1-9</sub> alkyl), -NHC(O)(C<sub>2-6</sub> alkenyl), -NHC(O)(C<sub>2-6</sub> alkynyl), -NHC(O)(C<sub>3-15</sub> cycloalkyl), -NHC(O)(C<sub>1-8</sub> haloalkyl), -NHC(O)(aryl), -NHC(O)(heteroaryl), -NHC(O)(heterocyclyl), -NHC(O)O(C<sub>1-9</sub> alkyl), -NHC(O)O(C<sub>2-6</sub> alkenyl), -NHC(O)O(C<sub>2-6</sub> alkynyl), -NHC(O)O(C<sub>3-15</sub> cycloalkyl), -NHC(O)O(C<sub>1-8</sub> haloalkyl), -NHC(O)O(aryl), -NHC(O)O(heteroaryl), -NHC(O)O(heterocyclyl), -
- 10 NHC(O)NH(C<sub>1-9</sub> alkyl), -NHC(O)NH(C<sub>2-6</sub> alkenyl), -NHC(O)NH(C<sub>2-6</sub> alkynyl), -NHC(O)NH(C<sub>3-15</sub> cycloalkyl), -NHC(O)NH(C<sub>1-8</sub> haloalkyl), -NHC(O)NH(aryl), -NHC(O)NH(heteroaryl), -NHC(O)NH(heterocyclyl), -SH, -S(C<sub>1-9</sub> alkyl), -S(C<sub>2-6</sub> alkenyl), -S(C<sub>2-6</sub> alkynyl), -S(C<sub>3-15</sub> cycloalkyl), -S(C<sub>1-8</sub> haloalkyl), -S(aryl), -S(heteroaryl), -S(heterocyclyl), -NHS(O)(C<sub>1-9</sub> alkyl), -N(C<sub>1-9</sub> alkyl)(S(O)(C<sub>1-9</sub> alkyl), -S(O)N(C<sub>1-9</sub> alkyl)<sub>2</sub>, -
- 15 S(O)(C<sub>1-9</sub> alkyl), -S(O)(NH)(C<sub>1-9</sub> alkyl), -S(O)(C<sub>2-6</sub> alkenyl), -S(O)(C<sub>2-6</sub> alkynyl), -S(O)(C<sub>3-15</sub> cycloalkyl), -S(O)(C<sub>1-8</sub> haloalkyl), -S(O)(aryl), -S(O)(heteroaryl), -S(O)(heterocyclyl), -S(O)<sub>2</sub>(C<sub>1-9</sub> alkyl), -S(O)<sub>2</sub>(C<sub>2-6</sub> alkenyl), -S(O)<sub>2</sub>(C<sub>2-6</sub> alkynyl), -S(O)<sub>2</sub>(C<sub>3-15</sub> cycloalkyl), -S(O)<sub>2</sub>(C<sub>1-8</sub> haloalkyl), -S(O)<sub>2</sub>(aryl), -S(O)<sub>2</sub>(heteroaryl), -S(O)<sub>2</sub>(heterocyclyl), -S(O)<sub>2</sub>NH(C<sub>1-9</sub> alkyl), or -S(O)<sub>2</sub>N(C<sub>1-9</sub> alkyl)<sub>2</sub>; wherein any alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is
- 20 optionally substituted with one or more halo, C<sub>1-9</sub> alkyl, C<sub>1-8</sub> haloalkyl, -OH, -NH<sub>2</sub>, -NH(C<sub>1-9</sub> alkyl), -NH(C<sub>3-15</sub> cycloalkyl), -NH(C<sub>1-8</sub> haloalkyl), -NH(aryl), -NH(heteroaryl), -NH(heterocyclyl), -N(C<sub>1-9</sub> alkyl)<sub>2</sub>, -N(C<sub>3-15</sub> cycloalkyl)<sub>2</sub>, -NHC(O)(C<sub>3-15</sub> cycloalkyl), -NHC(O)(C<sub>1-8</sub> haloalkyl), -NHC(O)(aryl), -NHC(O)(heteroaryl), -NHC(O)(heterocyclyl), -NHC(O)O(C<sub>1-9</sub> alkyl), -NHC(O)O(C<sub>2-6</sub> alkynyl), -NHC(O)O(C<sub>3-15</sub> cycloalkyl), -NHC(O)O(C<sub>1-8</sub> haloalkyl), -NHC(O)O(aryl), -NHC(O)O(heteroaryl), -
- 25 NHC(O)O(heterocyclyl), -NHC(O)NH(C<sub>1-9</sub> alkyl), -S(O)(NH)(C<sub>1-9</sub> alkyl), S(O)<sub>2</sub>(C<sub>1-9</sub> alkyl), -S(O)<sub>2</sub>(C<sub>3-15</sub> cycloalkyl), -S(O)<sub>2</sub>(C<sub>1-8</sub> haloalkyl), -S(O)<sub>2</sub>(aryl), -S(O)<sub>2</sub>(heteroaryl), -S(O)<sub>2</sub>(heterocyclyl), -S(O)<sub>2</sub>NH(C<sub>1-9</sub> alkyl), -S(O)<sub>2</sub>N(C<sub>1-9</sub> alkyl)<sub>2</sub>, -O(C<sub>3-15</sub> cycloalkyl), -O(C<sub>1-8</sub> haloalkyl), -O(aryl), -O(heteroaryl), -O(heterocyclyl), or -O(C<sub>1-9</sub> alkyl);
- 30 or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or deuterated analog thereof.

In one embodiment, R<sup>1</sup> is C<sub>3-10</sub> cycloalkyl optionally substituted with X<sup>1</sup>.

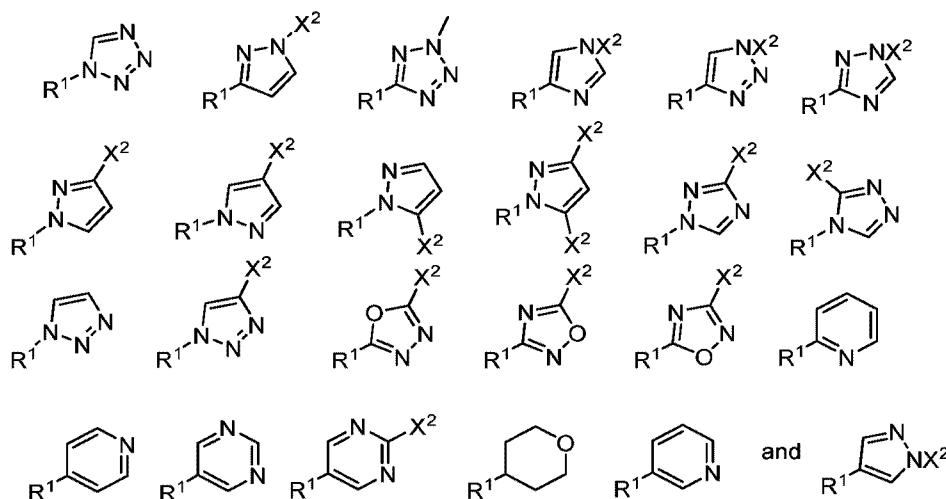
In another embodiment, R<sup>1</sup> is selected from cyclohexyl and bicyclo[2.2.2]octane.

In another embodiment,  $R^1$  is 4-12 membered heterocyclyl optionally substituted with  $X^1$ .

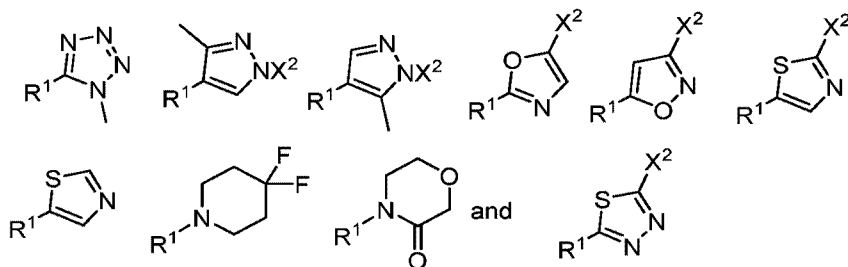
In another embodiment,  $R^1$  is tetrahydropyran.

In another embodiment,  $R^1$  is oxabicyclo[2.2.2]octane.

5 In one embodiment, "Het" is selected from:



In another embodiment, "Het" is:



In some embodiments, "Het" is substituted with  $X^2$ .

10 In one embodiment,  $X^2$  is halo, CN,  $C_{1-9}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{3-15}$  cycloalkyl,  $C_{1-8}$  haloalkyl, 4-12 membered heterocyclyl,  $-O-R^{12}$ ,  $C_{1-6}$  cyano alkyl,  $C_{1-6}$  alkyl ether,  $-OC(O)R^{12}$ ,  $-OC(O)OR^{12}$ , and  $-C(O)-N(R^{12})(R^{12})$ .

In an embodiment,  $X^2$  is selected from -F, CN,  $C_{1-4}$  alkyl,  $C_{1-8}$  haloalkyl,  $C_{3-4}$  cycloalkyl, and  $C_{1-3}$ cyanoalkyl.

15 In another embodiment,  $X^2$  is selected from methyl, ethyl,  $-CHF_2$ ,  $-CF_3$ , cyclopropyl,  $-CH_2CHF_2$ , and  $-CH_2CF_3$ .

In another embodiment,  $X^2$  is  $-\text{CHF}_2$ .

In another embodiment,  $R^2$  is  $\text{C}_{1-10}$  alkyl optionally substituted with  $Z^1$ .

In another embodiment,  $R^2$  is  $\text{C}_{1-10}$  alkyl optionally substituted with one or more  $-\text{F}$  or  $-\text{OH}$ , or combinations of  $\text{F}$  and  $\text{OH}$ .

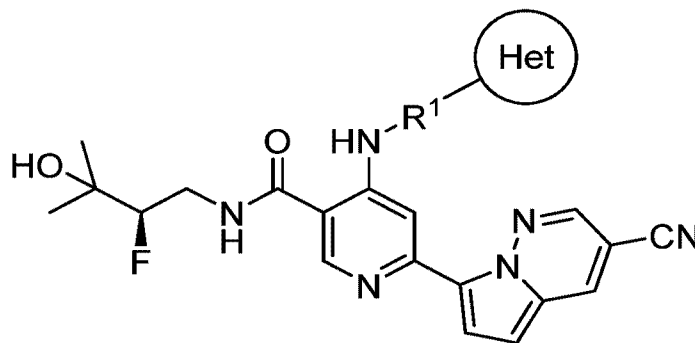
5 In another embodiment,  $R^2$  is  $\text{C}_{3-10}$  cycloalkyl optionally substituted with  $Z^1$ .

In another embodiment,  $R^2$  is  $\text{C}_{3-8}$  cycloalkyl optionally substituted with  $-\text{OH}$ ,  $-\text{N}(\text{R}^{12})\text{C}(\text{O})(\text{R}^{12})$ ,  $-\text{N}(\text{R}^{12})\text{C}(\text{O})\text{O}(\text{R}^{12})$ , or  $-\text{C}(\text{O})\text{N}(\text{R}^{12})(\text{R}^{12})$ .

In an embodiment,  $X^1$  is  $\text{F}$ .

In an embodiment,  $\text{Y}$  is  $\text{CN}$ .

10 In other embodiments, the disclosure provides a compound of Formula (Ia):



(Ia)

wherein,

$R^1$  is selected from  $\text{C}_{3-10}$  cycloalkyl optionally substituted with  $X^1$  and 4-12 membered  
15 heterocyclyl optionally substituted with  $X^1$ ;

wherein each  $X^1$  is independently oxo, halo,  $-\text{CN}$ ,  $\text{C}_{1-9}$  alkyl, and  $\text{C}_{3-15}$  cycloalkyl;

“Het” is selected from 5-10 membered heteroaryl optionally substituted with  $X^2$  and 4-12 membered heterocyclyl optionally substituted with  $X^2$ ;

20 wherein each  $X^2$  is selected from oxo, halo,  $\text{N}_3$ ,  $-\text{CN}$ ,  $\text{C}_{1-9}$  alkyl,  $\text{C}_{3-6}$  cycloalkyl  $\text{C}_{2-6}$  alkenyl,  $\text{C}_{2-6}$  alkynyl,  $\text{C}_{3-15}$  cycloalkyl,  $\text{C}_{1-8}$  haloalkyl, 4-12 membered heterocyclyl  $-\text{O}-\text{R}^{12}$ ,  $\text{C}_{1-6}$  cyano alkyl,  $\text{C}_{1-6}$  alkyl ether,  $-\text{OC}(\text{O})\text{R}^{12}$ ,  $-\text{OC}(\text{O})\text{OR}^{12}$ ,  $-\text{OC}(\text{O})-\text{N}(\text{R}^{12})(\text{R}^{12})$ , and  $-\text{C}(\text{O})\text{N}(\text{R}^{12})(\text{R}^{12})$ , wherein any alkyl, alkenyl, alkynyl, cycloalkyl, haloalkyl, or heterocyclyl is optionally substituted with  $Z^{1a}$ ;



8 haloalkyl), -NHC(O)O(aryl), -NHC(O)O(heteroaryl), -NHC(O)O(heterocyclyl), -  
 NHC(O)NH(C<sub>1-9</sub> alkyl), -NHC(O)NH(C<sub>2-6</sub> alkenyl), -NHC(O)NH(C<sub>2-6</sub> alkynyl), -  
 NHC(O)NH(C<sub>3-15</sub> cycloalkyl), -NHC(O)NH(C<sub>1-8</sub> haloalkyl), -NHC(O)NH(aryl), -  
 NHC(O)NH(heteroaryl), -NHC(O)NH(heterocyclyl), -SH, -S(C<sub>1-9</sub> alkyl), -S(C<sub>2-6</sub>  
 5 alkenyl), -S(C<sub>2-6</sub> alkynyl), -S(C<sub>3-15</sub> cycloalkyl), -S(C<sub>1-8</sub> haloalkyl), -S(aryl), -S(heteroaryl), -  
 S(heterocyclyl), -NHS(O)(C<sub>1-9</sub> alkyl), -N(C<sub>1-9</sub> alkyl)(S(O)(C<sub>1-9</sub> alkyl), -S(O)N(C<sub>1-9</sub> alkyl)<sub>2</sub>, -  
 S(O)(C<sub>1-9</sub> alkyl), -S(O)(NH)(C<sub>1-9</sub> alkyl), -S(O)(C<sub>2-6</sub> alkenyl), -S(O)(C<sub>2-6</sub> alkynyl), -S(O)(C<sub>3-15</sub>  
 cycloalkyl), -S(O)(C<sub>1-8</sub> haloalkyl), -S(O)(aryl), -S(O)(heteroaryl), -S(O)(heterocyclyl), -  
 S(O)<sub>2</sub>(C<sub>1-9</sub> alkyl), -S(O)<sub>2</sub>(C<sub>2-6</sub> alkenyl), -S(O)<sub>2</sub>(C<sub>2-6</sub> alkynyl), -S(O)<sub>2</sub>(C<sub>3-15</sub> cycloalkyl), -S(O)<sub>2</sub>(C<sub>1-8</sub>  
 10 haloalkyl), -S(O)<sub>2</sub>(aryl), -S(O)<sub>2</sub>(heteroaryl), -S(O)<sub>2</sub>(heterocyclyl), -S(O)<sub>2</sub>NH(C<sub>1-9</sub> alkyl),  
 or -S(O)<sub>2</sub>N(C<sub>1-9</sub> alkyl)<sub>2</sub>; wherein any alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is  
 optionally substituted with one or more halo, C<sub>1-9</sub> alkyl, C<sub>1-8</sub> haloalkyl, -OH, -NH<sub>2</sub>, -NH(C<sub>1-9</sub>  
 alkyl), -NH(C<sub>3-15</sub> cycloalkyl), -NH(C<sub>1-8</sub> haloalkyl), -NH(aryl), -  
 NH(heteroaryl), -NH(heterocyclyl), -N(C<sub>1-9</sub> alkyl)<sub>2</sub>, -N(C<sub>3-15</sub> cycloalkyl)<sub>2</sub>, -NHC(O)(C<sub>3-15</sub>  
 15 cycloalkyl), -NHC(O)(C<sub>1-8</sub> haloalkyl), -NHC(O)(aryl), -NHC(O)(heteroaryl), -  
 NHC(O)(heterocyclyl), -NHC(O)O(C<sub>1-9</sub> alkyl), -NHC(O)O(C<sub>2-6</sub> alkynyl), -NHC(O)O(C<sub>3-15</sub>  
 cycloalkyl), -NHC(O)O(C<sub>1-8</sub> haloalkyl), -NHC(O)O(aryl), -NHC(O)O(heteroaryl), -  
 NHC(O)O(heterocyclyl), -NHC(O)NH(C<sub>1-9</sub> alkyl), -S(O)(NH)(C<sub>1-9</sub> alkyl), S(O)<sub>2</sub>(C<sub>1-9</sub>  
 alkyl), -S(O)<sub>2</sub>(C<sub>3-15</sub> cycloalkyl), -S(O)<sub>2</sub>(C<sub>1-8</sub> haloalkyl), -S(O)<sub>2</sub>(aryl), -S(O)<sub>2</sub>(heteroaryl), -  
 20 S(O)<sub>2</sub>(heterocyclyl), -S(O)<sub>2</sub>NH(C<sub>1-9</sub> alkyl), -S(O)<sub>2</sub>N(C<sub>1-9</sub> alkyl)<sub>2</sub>, -O(C<sub>3-15</sub> cycloalkyl), -O(C<sub>1-8</sub>  
 haloalkyl), -O(aryl), -O(heteroaryl), -O(heterocyclyl), or -O(C<sub>1-9</sub> alkyl);

or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, or  
 deuterated analog thereof.

Also provided in the disclosure are pharmaceutical compositions comprising a  
 25 compound of Formula (I) or (Ia) or a pharmaceutically acceptable salt, stereoisomer, mixture of  
 stereoisomers or deuterated analog thereof, together with a pharmaceutically acceptable carrier.

The disclosure also provides methods of treating inflammatory conditions in a patient in  
 need of treatment. The method comprises administering a compound of Formula (I) or (Ia) as  
 described above to said patient in a therapeutically effective amount. In another embodiment, the  
 30 method comprises administering a composition comprising a therapeutically effective compound  
 of Formula (I) or (Ia) to a patient in need thereof.

In some embodiments, the inflammatory condition is selected from Inflammatory Bowel  
 Disease (IBD), Systemic Lupus Erythematosus (SLE), Psoriasis or Rheumatoid Arthritis.

## DETAILED DESCRIPTION OF THE INVENTION

### DEFINITIONS

The following description sets forth exemplary methods, parameters and the like. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

A dash (“-”) that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -C(O)NH<sub>2</sub> is attached through the carbon atom. A dash at the front or end of a chemical group is a matter of convenience; chemical groups may be depicted with or without one or more dashes without losing their ordinary meaning. A wavy line drawn through a line in a structure indicates a point of attachment of a group. Unless chemically or structurally required, no directionality is indicated or implied by the order in which a chemical group is written or named.

The prefix “C<sub>u-v</sub>” indicates that the following group has from u to v carbon atoms. For example, “C<sub>1-6</sub> alkyl” indicates that the alkyl group has from 1 to 6 carbon atoms.

Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter *per se*. In certain embodiments, the term “about” includes the indicated amount  $\pm 10\%$ . In other embodiments, the term “about” includes the indicated amount  $\pm 5\%$ . In certain other embodiments, the term “about” includes the indicated amount  $\pm 1\%$ . Also, the term “about X” includes description of “X”. Also, the singular forms “a” and “the” include plural references unless the context clearly dictates otherwise. Thus, e.g., reference to “the compound” includes a plurality of such compounds and reference to “the assay” includes reference to one or more assays and equivalents thereof known to those skilled in the art.

“Alkyl” refers to an unbranched or branched saturated hydrocarbon chain. As used herein, alkyl has 1 to 20 carbon atoms (i.e., C<sub>1-20</sub> alkyl), 1 to 8 carbon atoms (i.e., C<sub>1-8</sub> alkyl), 1 to 6 carbon atoms (i.e., C<sub>1-6</sub> alkyl), or 1 to 4 carbon atoms (i.e., C<sub>1-4</sub> alkyl). Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. When an alkyl residue having a specific number of carbons is named by chemical name or identified by molecular formula, all positional isomers having that number of carbons may be encompassed; thus, for example, “butyl” includes n-butyl (i.e., -(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), sec-butyl (i.e., -CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>), isobutyl (i.e., -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>) and tert-butyl (i.e., -C(CH<sub>3</sub>)<sub>3</sub>); and “propyl” includes n-propyl (i.e., -(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>) and isopropyl (i.e., -CH(CH<sub>3</sub>)<sub>2</sub>).

“Alkenyl” refers to an alkyl group containing at least one carbon-carbon double bond and having from 2 to 20 carbon atoms (i.e., C<sub>2-20</sub> alkenyl), 2 to 8 carbon atoms (i.e., C<sub>2-8</sub> alkenyl), 2 to 6 carbon atoms (i.e., C<sub>2-6</sub> alkenyl), or 2 to 4 carbon atoms (i.e., C<sub>2-4</sub> alkenyl). Examples of alkenyl groups include ethenyl, propenyl, butadienyl (including 1,2-butadienyl and 1,3-butadienyl).

“Alkynyl” refers to an alkyl group containing at least one carbon-carbon triple bond and having from 2 to 20 carbon atoms (i.e., C<sub>2-20</sub> alkynyl), 2 to 8 carbon atoms (i.e., C<sub>2-8</sub> alkynyl), 2 to 6 carbon atoms (i.e., C<sub>2-6</sub> alkynyl), or 2 to 4 carbon atoms (i.e., C<sub>2-4</sub> alkynyl). The term “alkynyl” also includes those groups having one triple bond and one double bond.

“Alkoxy” refers to the group “alkyl-O-”. Examples of alkoxy groups include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy.

“Haloalkoxy” refers to an alkoxy group as defined above, wherein one or more hydrogen atoms are replaced by a halogen.

“Alkylthio” refers to the group “alkyl-S-”.

“Amino” refers to the group -NR<sup>y</sup>R<sup>y</sup> wherein each R<sup>y</sup> is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, cycloalkyl or heteroaryl, each of which is optionally substituted, as defined herein.

“Aryl” refers to an aromatic carbocyclic group having a single ring (e.g., monocyclic) or multiple rings (e.g., bicyclic or tricyclic) including fused systems. As used herein, aryl has 6 to 20 ring carbon atoms (i.e., C<sub>6-20</sub> aryl), 6 to 12 carbon ring atoms (i.e., C<sub>6-12</sub> aryl), or 6 to 10 carbon ring atoms (i.e., C<sub>6-10</sub> aryl). Examples of aryl groups include phenyl, naphthyl, fluorenyl, and anthryl. Aryl, however, does not encompass or overlap in any way with heteroaryl defined below. If one or more aryl groups are fused with a heteroaryl, the resulting ring system is heteroaryl. If one or more aryl groups are fused with a heterocyclyl, the resulting ring system is heterocyclyl.

“Cyano” refers to the group -CN.

“Keto” or “oxo” refers to a group =O.

“Carbamoyl” refers to both an “O-carbamoyl” group which refers to the group -O-C(O)NR<sup>y</sup>R<sup>z</sup> and an “N-carbamoyl” group which refers to the group -NR<sup>y</sup>C(O)OR<sup>z</sup>, wherein R<sup>y</sup> and R<sup>z</sup> are independently selected from the group consisting of hydrogen, alkyl, aryl, haloalkyl, or heteroaryl; each of which may be optionally substituted.

“Carboxyl” refers to -C(O)OH.

“Ester” refers to both -OC(O)R and -C(O)OR, wherein R is a substituent; each of which may be optionally substituted, as defined herein.

“Cycloalkyl” refers to a saturated or partially unsaturated cyclic alkyl group having a single ring or multiple rings including fused, bridged, and spiro ring systems. The term “cycloalkyl” includes cycloalkenyl groups (i.e., the cyclic group having at least one double bond). As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (i.e., C<sub>3-20</sub> cycloalkyl), 3 to 12 ring carbon atoms (i.e., C<sub>3-12</sub> cycloalkyl), 3 to 10 ring carbon atoms (i.e., C<sub>3-10</sub> cycloalkyl), 3 to 8 ring carbon atoms (i.e., C<sub>3-8</sub> cycloalkyl), or 3 to 6 ring carbon atoms (i.e., C<sub>3-6</sub> cycloalkyl). Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

“Halogen” or “halo” includes fluoro, chloro, bromo, and iodo. “Haloalkyl” refers to an unbranched or branched alkyl group as defined above, wherein one or more hydrogen atoms are replaced by a halogen. For example, where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached. Dihaloalkyl and trihaloalkyl refer to alkyl substituted with two (“di”) or three (“tri”) halo groups, which may be, but are not necessarily, the same halogen. Examples of haloalkyl include difluoromethyl (-CHF<sub>2</sub>) and trifluoromethyl (-CF<sub>3</sub>).

“Heteroalkyl” refers to an alkyl group in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatomic group. The term “heteroalkyl” includes unbranched or branched saturated chain having carbon and heteroatoms. By way of example, 1, 2 or 3 carbon atoms may be independently replaced with the same or different heteroatomic group. Heteroatomic groups include, but are not limited to, -NR-, -O-, -S-, -S(O)-, -S(O)<sub>2</sub>-, and the like, where R is H, alkyl, aryl, cycloalkyl, heteroalkyl, heteroaryl or heterocyclyl, each of which may be optionally substituted. Examples of heteroalkyl groups include -OCH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>3</sub>, -SCH<sub>3</sub>, -CH<sub>2</sub>SCH<sub>3</sub>, -NRCH<sub>3</sub>, and -CH<sub>2</sub>NRCH<sub>3</sub>, where R is hydrogen, alkyl, aryl, arylalkyl, heteroalkyl, or heteroaryl, each of which may be optionally substituted. As used herein, heteroalkyl include 1 to 10 carbon atoms, 1 to 8 carbon atoms, or 1 to 4 carbon atoms; and 1 to 3 heteroatoms, 1 to 2 heteroatoms, or 1 heteroatom.

“Heteroaryl” refers to an aromatic group having a single ring, multiple rings, or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. As used herein, heteroaryl includes 1 to 20 ring carbon atoms (i.e., C<sub>1-20</sub> heteroaryl), 3 to 12 ring carbon atoms (i.e., C<sub>3-12</sub> heteroaryl), or 3 to 8 carbon ring atoms (i.e., C<sub>3-8</sub>

heteroaryl); and 1 to 5 heteroatoms, 1 to 4 heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen, and sulfur. Examples of heteroaryl groups include pyrimidinyl, purinyl, pyridyl, pyridazinyl, benzothiazolyl, and pyrazolyl. Examples of the fused-heteroaryl rings include, but are not limited to, benzo[d]thiazolyl, quinolinyl, isoquinolinyl, benzo[b]thiophenyl, indazolyl, benzo[d]imidazolyl, pyrazolo[1,5-a]pyridinyl, and imidazo[1,5-a]pyridinyl, where the heteroaryl can be bound via either ring of the fused system. Any aromatic ring, having a single or multiple fused rings, containing at least one heteroatom, is considered a heteroaryl regardless of the attachment to the remainder of the molecule (i.e., through any one of the fused rings). Heteroaryl does not encompass or overlap with aryl as defined above.

“Heterocyclyl” refers to a saturated or unsaturated cyclic alkyl group, with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur. The term “heterocyclyl” includes heterocycloalkenyl groups (i.e., the heterocyclyl group having at least one double bond), bicyclic heterocyclyl groups, bridged-heterocyclyl groups, fused-heterocyclyl groups, and spiro-heterocyclyl groups. A heterocyclyl may be a single ring or multiple rings wherein the multiple rings may be fused, bridged, or spiro. Any non-aromatic ring containing at least one heteroatom is considered a heterocyclyl, regardless of the attachment (i.e., can be bound through a carbon atom or a heteroatom). Further, the term heterocyclyl is intended to encompass any non-aromatic ring containing at least one heteroatom, which ring may be fused to an aryl or heteroaryl ring, regardless of the attachment to the remainder of the molecule. As used herein, heterocyclyl has 2 to 20 ring atoms (i.e., 4-20 membered heterocyclyl), 2 to ring atoms (i.e., 4-12 membered heterocyclyl), 4 to 10 ring atoms (i.e., 4-10 membered heterocyclyl), 4 to 8 ring atoms (i.e., 4-8 membered heterocyclyl), or 4 to 6 ring carbon atoms (i.e., 4-6 membered heterocyclyl); having 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, sulfur or oxygen. A heterocyclyl may contain one or more oxo and/or thioxo groups. Examples of heterocyclyl groups include pyrrolidinyl, piperidinyl, piperazinyl, oxetanyl, dioxolanyl, azetidiny, azetidiny, morpholinyl, thiomorpholinyl, 4-7 membered sultam, 4-7 membered cyclic carbamate, 4-7 membered cyclic carbonate, 4-7 membered cyclic sulfide and morpholinyl. As used herein, the term “bridged- heterocyclyl” refers to a four- to ten-membered cyclic moiety connected at two non-adjacent atoms of the heterocyclyl with one or more (e.g., 1 or 2) four- to ten-membered cyclic moiety having at least one heteroatom where each heteroatom is independently selected from nitrogen, oxygen, and sulfur. As used herein, bridged- heterocyclyl includes bicyclic and tricyclic ring systems. Also used herein, the term

“spiro-heterocyclyl” refers to a ring system in which a three- to ten-membered heterocyclyl has one or more additional ring, wherein the one or more additional ring is three- to ten-membered cycloalkyl or three- to ten-membered heterocyclyl, where a single atom of the one or more additional ring is also an atom of the three- to ten-membered heterocyclyl. Examples of the spiro-heterocyclyl rings include bicyclic and tricyclic ring systems, such as 2-oxa-7-azaspiro[3.5]nonanyl, 2-oxa-6-azaspiro[3.4]octanyl, and 6-oxa-1-azaspiro[3.3]heptanyl. Examples of the fused-heterocyclyl rings include, but are not limited to, 1,2,3,4-tetrahydroisoquinolanyl, 1-oxo-1,2,3,4-tetrahydroisoquinolanyl, 1-oxo-1,2-dihydroisoquinolanyl, 4,5,6,7-tetrahydrothieno[2,3-c]pyridinyl, indolinyl, and isoindolinyl, where the heterocyclyl can be bound via either ring of the fused system. As used herein, a bicyclic heterocyclyl group is a heterocyclyl group attached at two points to another cyclic group, wherein the other cyclic group may itself be a heterocyclic group, or a carbocyclic group.

As used herein, the term “nitrogen or sulfur containing heterocyclyl” means a heterocyclyl moiety that contains at least one nitrogen atom or at least one sulfur atom, or both a nitrogen atom and a sulfur atom within the ring structure. It is to be understood that other heteroatoms, including oxygen, may be present in addition to the nitrogen, sulfur, or combinations thereof. Examples of nitrogen or sulfur containing heterocyclyls include morpholinyl, thiomorpholinyl, thiazolyl, isothiazolyl, oxazolidinone 1,2 dithiolyl, piperidinyl, piperazinyl, and the like.

“Hydroxy” or “hydroxyl” refers to the group -OH. “Hydroxyalkyl” refers to an unbranched or branched alkyl group as defined above, wherein one or more hydrogen atoms are replaced by a hydroxyl.

“Nitro” refers to the group -NO<sub>2</sub>.

“Sulfonyl” refers to the group -S(O)<sub>2</sub>R, where R is a substituent, or a defined group.

“Alkylsulfonyl” refers to the group -S(O)<sub>2</sub>R, where R is a substituent, or a defined group.

“Alkylsulfinyl” refers to the group -S(O)R, where R is a substituent, or a defined group.

“Thiocyanate” -SCN.

“Thiol” refers to the group -SR, where R is a substituent, or a defined group.

“Thioxo” or “thione” refer to the group (=S) or (S).

Certain commonly used alternative chemical names may be used. For example, a divalent group such as a divalent “alkyl” group, a divalent “aryl” group, etc., may also be referred to as an “alkylene” group or an “alkylenyl” group, an “arylene” group or an “arylenyl”

group, respectively. Also, unless indicated explicitly otherwise, where combinations of groups are referred to herein as one moiety, e.g., arylalkyl, the last mentioned group contains the atom by which the moiety is attached to the rest of the molecule.

The terms “optional” or “optionally” means that the subsequently described event or  
5 circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. Also, the term “optionally substituted” refers to any one or more hydrogen atoms on the designated atom or group may or may not be replaced by a moiety other than hydrogen. “Optionally substituted” may be zero to the maximum number of possible substitutions, and each occurrence is independent. When the  
10 term “substituted” is used, then that substitution is required to be made at a substitutable hydrogen atom of the indicated substituent. An optional substitution may be the same or different from a (required) substitution.

When a moiety is “optionally substituted,” and reference is made to a general term, such as any “alkyl,” “alkenyl,” “alkynyl,” “haloalkyl,” “cycloalkyl,” “aryl” or “heteroaryl,” then the  
15 general term can refer to any antecedent specifically recited term, such as (C<sub>1-3</sub> alkyl), (C<sub>4-6</sub> alkyl), -O(C<sub>1-4</sub> alkyl), (C<sub>3-10</sub> cycloalkyl), O-(C<sub>3-10</sub> cycloalkyl) and the like. For example, “any aryl” includes both “aryl” and “-O(aryl)” as well as examples of aryl, such as phenyl or naphthyl and the like. Also, the term “any heterocyclyl” includes both the terms “heterocyclyl” and O-(heterocyclyl),” as well as examples of heterocyclyls, such as oxetanyl, tetrahydropyranyl,  
20 morpholino, piperidinyl and the like. In the same manner, the term “any heteroaryl” includes the terms “heteroaryl” and “O-(heteroaryl),” as well as specific heteroaryls, such as pyridine and the like.

Some of the compounds exist as tautomers. Tautomers are in equilibrium with one  
25 another. For example, amide containing compounds may exist in equilibrium with imidic acid tautomers. Regardless of which tautomer is shown, and regardless of the nature of the equilibrium among tautomers, the compounds are understood by one of ordinary skill in the art to comprise both amide and imidic acid tautomers. Thus, the amide containing compounds are understood to include their imidic acid tautomers. Likewise, the imidic acid containing  
30 compounds are understood to include their amide tautomers.

Any formula or structure given herein, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be

incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as, but not limited to  $^2\text{H}$  (deuterium, D),  $^3\text{H}$  (tritium),  $^{11}\text{C}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{F}$ ,  $^{31}\text{P}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{36}\text{Cl}$  and  $^{125}\text{I}$ . Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as  $^3\text{H}$ ,  $^{13}\text{C}$  and  $^{14}\text{C}$  are incorporated. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in radioactive treatment of patients.

The disclosure also includes “deuterated analogues” of compounds of Formula (I) in which from 1 to n hydrogens attached to a carbon atom is/are replaced by deuterium, in which n is the number of hydrogens in the molecule. Such compounds exhibit increased resistance to metabolism and are thus useful for increasing the half-life of any compound of Formula (I) when administered to a mammal, particularly a human. See, for example, Foster, “Deuterium Isotope Effects in Studies of Drug Metabolism,” Trends Pharmacol. Sci. 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogens have been replaced by deuterium.

Deuterium labelled or substituted therapeutic compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life, reduced dosage requirements and/or an improvement in therapeutic index. An  $^{18}\text{F}$  labeled compound may be useful for PET or SPECT studies. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. It is understood that deuterium in this context is regarded as a substituent in the compound of Formula I.

The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as “H” or “hydrogen”, the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium.

In many cases, the compounds of this disclosure are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

5 Provided are also pharmaceutically acceptable salts, hydrates, solvates, tautomeric forms, polymorphs, and prodrugs of the compounds described herein. “Pharmaceutically acceptable” or “physiologically acceptable” refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

The term “pharmaceutically acceptable salt” of a given compound refers to salts that retain the biological effectiveness and properties of the given compound, and which are not biologically or otherwise undesirable. “Pharmaceutically acceptable salts” or “physiologically acceptable salts” include, for example, salts with inorganic acids and salts with an organic acid. In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare nontoxic pharmaceutically acceptable addition salts. Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, and the like. Likewise, pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases include, by way of example only, sodium, potassium, lithium, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines (i.e.,  $\text{NH}_2(\text{alkyl})$ ), dialkyl amines (i.e.,  $\text{HN}(\text{alkyl})_2$ ), trialkyl amines (i.e.,  $\text{N}(\text{alkyl})_3$ ), substituted alkyl amines (i.e.,  $\text{NH}_2(\text{substituted alkyl})$ ), di(substituted alkyl) amines (i.e.,  $\text{HN}(\text{substituted alkyl})_2$ ), tri(substituted alkyl) amines (i.e.,  $\text{N}(\text{substituted alkyl})_3$ ), alkenyl amines (i.e.,  $\text{NH}_2(\text{alkenyl})$ ), dialkenyl amines (i.e.,  $\text{HN}(\text{alkenyl})_2$ ), trialkenyl amines (i.e.,  $\text{N}(\text{alkenyl})_3$ ), substituted alkenyl amines (i.e.,  $\text{NH}_2(\text{substituted alkenyl})$ ), di(substituted alkenyl) amines (i.e.,  $\text{HN}(\text{substituted alkenyl})_2$ ), tri(substituted alkenyl) amines (i.e.,  $\text{N}(\text{substituted alkenyl})_3$ ), mono-

di- or tri- cycloalkyl amines (i.e.,  $\text{NH}_2(\text{cycloalkyl})$ ,  $\text{HN}(\text{cycloalkyl})_2$ ,  $\text{N}(\text{cycloalkyl})_3$ ), mono-, di- or tri- arylamines (i.e.,  $\text{NH}_2(\text{aryl})$ ,  $\text{HN}(\text{aryl})_2$ ,  $\text{N}(\text{aryl})_3$ ), or mixed amines, etc. Specific examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, 5 piperazine, piperidine, morpholine, N-ethylpiperidine, and the like.

The term “substituted” means that any one or more hydrogen atoms on the designated atom or group is replaced with one or more substituents other than hydrogen, provided that the designated atom’s normal valence is not exceeded. The one or more substituents include, but are not limited to, alkyl, alkenyl, alkynyl, alkoxy, acyl, amino, amido, amidino, aryl, azido, 10 carbamoyl, carboxyl, carboxyl ester, cyano, guanidino, halo, haloalkyl, haloalkoxy, heteroalkyl, heteroaryl, heterocyclyl, hydroxy, hydrazino, imino, oxo, nitro, alkylsulfinyl, sulfonic acid, alkylsulfonyl, thiocyanate, thiol, thione, or combinations thereof. Polymers or similar indefinite structures arrived at by defining substituents with further substituents appended ad infinitum (e.g., a substituted aryl having a substituted alkyl which is itself substituted with a substituted 15 aryl group, which is further substituted by a substituted heteroalkyl group, etc.) are not intended for inclusion herein. Unless otherwise noted, the maximum number of serial substitutions in compounds described herein is three. For example, serial substitutions of substituted aryl groups with two other substituted aryl groups are limited to ((substituted aryl)substituted aryl) substituted aryl. Similarly, the above definitions are not intended to include impermissible 20 substitution patterns (e.g., methyl substituted with 5 fluorines or heteroaryl groups having two adjacent oxygen ring atoms). Such impermissible substitution patterns are well known to the skilled artisan. When used to modify a chemical group, the term “substituted” may describe other chemical groups defined herein. Unless specified otherwise, where a group is described as optionally substituted, any substituents of the group are themselves unsubstituted. For example, 25 in some embodiments, the term “substituted alkyl” refers to an alkyl group having one or more substituents including hydroxyl, halo, alkoxy, cycloalkyl, heterocyclyl, aryl, and heteroaryl. In other embodiments, the one or more substituents may be further substituted with halo, alkyl, haloalkyl, hydroxyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is substituted. In other embodiments, the substituents may be further substituted with halo, alkyl, 30 haloalkyl, alkoxy, hydroxyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is unsubstituted. One skilled in the art will recognize that substituents and other moieties of the compounds of the generic formula herein should be selected in order to provide a compound which is sufficiently stable to provide a pharmaceutically useful compound which can be formulated into an acceptably stable pharmaceutical composition. Compounds which have such stability are

contemplated as falling within the scope of the present invention. It should be understood by one skilled in the art that any combination of the definitions and substituents described above should not result in an inoperable species or compound.

As used herein, “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

A “solvate” is formed by the interaction of a solvent and a compound. Solvates of salts of the compounds described herein are also provided. Hydrates of the compounds described herein are also provided.

### **COMBINATIONS**

Patients being treated by administration of the IRAK4 inhibitors of the disclosure often exhibit diseases or conditions that benefit from treatment with other therapeutic agents. These diseases or conditions can be of an inflammatory nature or can be related to cancer, metabolic disorders, gastrointestinal disorders and the like. Thus, one aspect of the disclosure is a method of treating an inflammation related disease or condition, or a metabolic disorder, gastrointestinal disorder, or cancer and the like comprising administering a compound of the in combination with one or more compounds useful for the treatment of such diseases to a subject, particularly a human subject, in need thereof.

In some embodiments, a compound of the present disclosure is co-formulated with the additional one or more active ingredients. In some embodiments, the other active ingredient is administered at approximately the same time, in a separate dosage form. In some embodiments, the other active ingredient is administered sequentially, and may be administered at different times in relation to a compound of the present disclosure.

### **COMBINATIONS FOR INFLAMMATORY DISEASES AND CONDITIONS**

For example, a compound of the present disclosure may be combined with one or more 5-Lipoxygenase inhibitors, Acetylcholinesterase inhibitors, Acetyl-CoA carboxylase (ACC) inhibitors, ACTH receptor agonists, Activin receptor antagonists, Acyltransferase inhibitors, Adrenocorticotrophic hormone ligands, AKT1 gene inhibitors, Alkaline phosphatase

modulators, Alkaline phosphatase stimulators, Androgen receptor agonists, Apolipoprotein C3 antagonists, ASK1 kinase inhibitors, Bactericidal permeability protein stimulators, Beta adrenoceptor antagonists, Beta-glucuronidase inhibitors, B-lymphocyte antigen CD20 inhibitors, Bradykinin receptor modulators, BTK kinase inhibitors, Calcineurin inhibitors, Calcium channel

5 inhibitors, Cannabinoid CB1 receptor modulators, Cannabinoid CB2 receptor modulators, Cannabinoid receptor antagonists, Cannabinoid receptor modulators, Caspase inhibitors, Cathepsin S inhibitors, CCN protein stimulators, CCR3 chemokine antagonists, CCR5 chemokine antagonists, CCR9 chemokine antagonists, CD3 modulators, CD40 ligand inhibitors, CD40 ligand receptor antagonists, CD49b antagonists, CD49d antagonists, CD89 agonists, Cell

10 adhesion molecule inhibitors, Chemokine CXC ligand inhibitors, CHST15 gene inhibitors, Collagen modulators, CSF-1 agonists, CSF-1 antagonists, CXC10 chemokine ligand inhibitors, CXCR2 chemokine antagonists, Cyclic GMP phosphodiesterase inhibitors, Cyclooxygenase 2 inhibitors, Cyclooxygenase inhibitors, Cyclooxygenase stimulators, Cytochrome P450 3A4 inhibitors, Cytotoxic T-lymphocyte protein-4 stimulators, Dihydroceramide delta 4 desaturase

15 inhibitors, Dihydroorotate dehydrogenase inhibitors, DNA polymerase inhibitors, DPP-4 inhibitors, EGFR family tyrosine kinase receptor modulators, Eosinophil peroxidase inhibitors, Eotaxin ligand inhibitors, EP4 prostanoid receptor agonists, Epidermal growth factor agonists, Epidermal growth factor ligands, Estrogen receptor beta agonists, Factor XIII agonists, FGF-10 ligands, FGF2 receptor agonists, Fractalkine ligand inhibitors, Free fatty acid receptor 2

20 antagonists, FXR agonists, GATA 3 transcription factor inhibitors, Glucagon-like peptide 1 agonists, Glucagon-like peptide 2 agonists, Glucocorticoid agonists, GM-CSF receptor agonists, G-protein coupled receptor 84 antagonists, Guanylate cyclase receptor agonists, Histamine H2 receptor antagonists, Histone acetyltransferase inhibitors, Histone deacetylase inhibitors, HLA class II antigen modulators, Hydrolase inhibitors, HSD17 $\beta$ 13 inhibitors, ICAM1 gene inhibitors,

25 ICAM-1 inhibitors, IL1 gene inhibitors, IL-10 agonists, IL10 gene stimulators, IL-11 agonists, IL-12 antagonists, IL12 gene inhibitors, IL-13 antagonists, IL-17 antagonists, IL-2 antagonists, IL-2 receptor alpha subunit inhibitors, IL-21 antagonists, IL-23 antagonists, IL-6 antagonists, IL6 gene inhibitors, IL-6 receptor modulators, IL-7 antagonists, IL-8 antagonists,

Immunoglobulin G1 agonists, Immunoglobulin G2 modulators, Inosine monophosphate

30 dehydrogenase inhibitors, Insulin sensitizers, Integrin alpha-4/beta-1 antagonists, Integrin alpha-4/beta-7 antagonists, Integrin alpha-E antagonists, Integrin antagonists, Integrin beta-7 antagonists, Interferon beta ligands, Interleukin 17E ligand inhibitors, Interleukin ligand inhibitors, Interleukin receptor 17A antagonists, Interleukin receptor 17B antagonists, Interleukin-1 beta ligands, Interleukin-1 beta ligand modulators, Interleukin-6 ligand inhibitors,

JAK tyrosine kinase inhibitors, Jak1 tyrosine kinase inhibitors, JAK2 gene inhibitors, Jak3  
 tyrosine kinase inhibitors, Jun N terminal kinase inhibitors, LanC like protein 2 modulators,  
 Leukotriene BLT receptor antagonists, Lipoxygenase modulators, L-Selectin antagonists,  
 MAdCAM inhibitors, Matrix metalloprotease inhibitors, Matrix metalloprotease modulators,  
 5 Melanocortin agonists, Membrane copper amine oxidase inhibitors, Metalloprotease-2  
 inhibitors, Metalloprotease-9 inhibitors, MIP 3 alpha ligand inhibitors, Mitochondrial 10 kDa  
 heat shock protein stimulators, Monocyte differentiation antigen CD14 inhibitors, mTOR  
 inhibitors, Mucin stimulators, NAD-dependent deacetylase sirtuin-1 stimulators, Natriuretic  
 peptide receptor C agonists, Neuregulin-4 ligands, Nicotinic acetylcholine receptor agonists,  
 10 Nicotinic ACh receptor alpha 4 subunit modulators, Nicotinic ACh receptor alpha 7 subunit  
 stimulators, Nicotinic ACh receptor beta 2 subunit modulators, NK1 receptor antagonists,  
 NKG2 D activating NK receptor antagonists, Nuclear factor kappa B inhibitors, Opioid growth  
 factor receptor agonists, Opioid receptor antagonists, Opioid receptor delta antagonists,  
 Oxidoreductase inhibitors, P2X7 purinoceptor agonists, p38 MAP kinase inhibitors, PARP  
 15 inhibitors, PDE 4 inhibitors, PDGF receptor agonists, Phagocytosis stimulating peptide  
 modulators, Phospho MurNAc pentapeptide transferase inhibitors, Phospholipase A2 inhibitors,  
 Platelet activating factor receptor antagonists, Potassium channel inhibitors, PPAR alpha  
 agonists, PPAR delta agonists, PPAR gamma agonists, Protein CYR61 stimulators, Protein  
 fimH inhibitors, Protein kinase C alpha inhibitors, Protein kinase C beta inhibitors, Protein  
 20 kinase C delta inhibitors, Protein kinase C epsilon inhibitors, Protein kinase C eta inhibitors,  
 Protein kinase C theta inhibitors, Protein kinase G inhibitors, Protein kinase inhibitors, P-  
 selectin glycoprotein ligand-1 inhibitors, PurH purine biosynthesis protein inhibitors, Retinoic  
 acid receptor alpha agonists, Retinoic acid receptor beta agonists, Retinoid receptor agonists,  
 RNA polymerase inhibitors, SMAD-7 inhibitors, Sodium channel inhibitors, Somatostatin  
 25 receptor agonists, Sphingosine 1 phosphate phosphatase 1 stimulators, Sphingosine 1 phosphate  
 phosphatase modulators, Sphingosine kinase 1 inhibitors, Sphingosine kinase 2 inhibitors,  
 Sphingosine-1-phosphate receptor-1 agonists, Sphingosine-1-phosphate receptor-1 antagonists,  
 Sphingosine-1-phosphate receptor-1 modulators, Sphingosine-1-phosphate receptor-5  
 modulators, STAT3 gene inhibitors, STAT-3 inhibitors, STAT-4 inhibitors, Stem cell antigen-1  
 30 inhibitors, Superoxide dismutase modulators, Superoxide dismutase stimulators, SYK kinase  
 inhibitors, T cell surface glycoprotein CD28 inhibitors, TGF beta 1 ligand inhibitors, Thymulin  
 agonists, THR- $\beta$  agonists, TLR-2 antagonists, TLR-4 antagonists, TLR-9 agonists, TNF alpha  
 ligand inhibitors, TNF alpha ligand modulators, TNF antagonists, TPL2 kinase inhibitors,  
 Trefoil factor modulators, Tryptase inhibitors, Tryptophan 5-hydroxylase inhibitors, Tumor

necrosis factor 14 ligand modulators, TYK2 kinase inhibitors, Type I TNF receptor antagonists, Type II TNF receptor modulators, Unspecified growth factor receptor modulators, Vanilloid VR1 agonists, Vitamin D3 receptor agonists, Zonulin inhibitors, abatacept; acemannan; adalimumab; DCCT-10; apremilast; AST-120; balsalazide; balsalazide sodium ; basiliximab; 5 beclomethasone dipropionate; budesonide; D-9421; budesonide MMX; catridecacog; certolizumab pegol; Clostridium butyricum; etanercept; fingolimod; glatiramer acetate; golimumab; infliximab; infliximab biosimilar; infliximab follow-on biologic; interferon beta-1a.; lenalidomide; mesalazine ; GED-0001; AJG-501; metenkefalin acetate with tridecactide acetat, mycophenolate mofetil; naltrexone; natalizumab; nitazoxanide; olsalazine; oprelvekin; 10 propionyl-L-carnitine; recombinant interferon beta-1a; remestemcel-L; rifaximin; rituximab; ropivacaine; rosiglitazone; sargramostim; secukinumab; SPD-480; tacrolimus; tamibarotene; teduglutide; thalidomide; tocilizumab ; RO-4877533; tofacitinib ; CP-690550; Trichuris suis ova; ASP-1002; ustekinumab; valganciclovir; vedolizumab; zileuton; anti-CD3 imaging agent (antibody fragment, cancer/autoimmune disease), ImaginAb; AVX-470; ciclosporin; CXCR1/2 15 ligands mAb (immunology), Eli Lilly; FFP-102; GSK-3050002; INN-108; IR-777; SGM-1019; peg-ilodecakin; PF-06480605; PF-06651600; SER-287; Syn-1002; Thetanix; tolerogenic dendritic cell therapy TOP-1288; VBY-036; VBY-129; 946414-98-8; BMS-936557; 99mTc-annexin V-128; ABC-294640; abrilumab; Alequel; AMG-139; amiselimod; APD-334; ASP-3291; beclomethasone dipropionate; bertilimumab; ciclosporin; clazakizumab; DLX-105; 20 dolcanatide; E-6011; ETX-201; FFP-104; filgotinib; foralumab; GED-0507-34-Levo; givinostat; GLPG-0974; GLPG-1205; iberogast N (ulcerative colitis), Bayer; BAY98-7410; INV-103; JNJ-40346527; K(D)PT; KAG-308; KHK-4083; KRP-203; larazotide acetate; CB-01-05-MMX; LY-3074828; mesalamine with N-acetylcysteine ; midismase; molgramostim follow on biologic with fosfomycin with carbapenem , Reponex; multipotent adult progenitor cell therapy 25 (ischemia/cerebral palsy), Athersys/ Healios; NN-8828; olokizumab; OvaSave; P-28-GST; PDA-002; PF-4236921; PF-547659; prednisolone; PUR-0110; QBECO; RBX-2660; repurposed naltrexone; JKB-122; SB-012; sotrastaurin; STNM-01; TAK-114; tetomilast; Debio-0512; TRK-170; TRX-318; vatelizumab; VB-201; ZP-1848; zucapsaicin ; ABT-494; alicaforsen; Ampion; BI-655066; briakinumab; cannabidiol; carotegast methyl; cobitolimod; dexamethasone 30 sodium phosphate; elafibranor; etrolizumab; GS-5745; HMPL-004; LP-02; mesalazine; metronidazole mongersen; ocrelizumab; ozanimod; peficitinib; RHB-104; rifaximin ; tildrakizumab; tralokinumab; brodalumab; laquinimod; plecanatide; telotristat etiprate; infliximab biosimilar, Samsung Bioepis; AZD-058; and rifabutin with clarithromycin and further with clofazimine.

Also, the following non-exhaustive list of classes of compounds and compounds may be combined with a compound of the present disclosure: 5-Lipoxygenase inhibitors, such as zileuton, etalocibm FPL-64170, E-3040, and BU-4601A; Acetylcholinesterase inhibitors, such as BL-7040; ACTH receptor agonists, such as metenkefalin acetate with tridecactide acetate, and FAR-404; Activin receptor antagonists such as follistatin; Acyltransferase inhibitors such as AZD-0585; Adrenocorticotrophic hormone ligands, such as metenkefalin acetate with tridecactide acetate, and FAR-404; AKT1 gene inhibitors, such as vidofludimus; Alkaline phosphatase modulators such as recombinant human alkaline phosphatase (oral, ulcerative colitis), AM-Pharma; Alkaline phosphatase stimulators such as bovine alkaline phosphatase; Androgen receptor agonists, such as PB-005; Apolipoprotein C3 antagonists, such as AZD-0585; Bactericidal permeability protein stimulators, such as opebacan; Beta adrenoceptor antagonists, such as NM-001; Beta-glucuronidase inhibitors, such as KD-018; B-lymphocyte antigen CD20 inhibitors, such as ocrelizumab, rituximab; Bradykinin receptor modulators, such as givinostat; Calcineurin inhibitors, such as tacrolimus, ciclosporin; Calcium channel inhibitors, such as clotrimazole; Cannabinoid CB1 receptor modulators, such as GWP42003-P, cannabidiol; Cannabinoid CB2 receptor modulators, such as GWP42003-P, cannabidiol; Cannabinoid receptor antagonists, such as fingolimod; Cannabinoid receptor modulators, such as GWP42003-P, cannabidiol; Cathepsin S inhibitors, such as VBY-129, VBY-036; CCN protein stimulators, such as CSA-13; CCR3 chemokine antagonists, such as bertilimumab; CCR5 chemokine antagonists, such as HGS-1025; CCR9 chemokine antagonists, such as MLN-3126, vercirmon, CCX-025; CD3 modulators, such as visilizumab; CD40 ligand inhibitors, such as FFP-104; CD40 ligand receptor antagonists, such as FFP-104, FFP-102, toralizumab; CD49b antagonists, such as vatelizumab; CD49d antagonists, such as ELND-004; CD89 agonists, such as HF-1020; Cell adhesion molecule inhibitors, such as natalizumab, alicaforsen (intravenous), ASP-2002, ISIS-2302; Chemokine CXC ligand inhibitors, such as CXCR1/2 ligands mAb (immunology), Eli Lilly; CHST15 gene inhibitors, such as STNM-01; Collagen modulators, such as adipose-derived stem cell therapy (Celution System), Cytori, DCCT-10; CSF-1 agonists, such as sargramostim, molgramostim follow on biologic with fosfomycin with carbapenem (intraintestinal, Crohn's disease), Reponex; CSF-1 antagonists, such as JNJ-40346527; CXC10 chemokine ligand inhibitors, such as 946414-98-8, BMS-936557; CXCR2 chemokine antagonists, such as elubrixin; Cyclic GMP phosphodiesterase inhibitors, such as CEL-031; Cyclooxygenase 2 inhibitors, such as P-54; Cyclooxygenase inhibitors, such as mesalazine, 4-aminosalicylate sodium, AJG-501, AGI-022; Cyclooxygenase stimulators, such as nicotine polacrilex; Cytochrome P450 3A4 inhibitors, such as KD-018; Cytotoxic T-lymphocyte protein-

4 stimulators, such as abatacept; Dihydroceramide delta 4 desaturase inhibitors, such as ABC-294640; Dihydroorotate dehydrogenase inhibitors, such as vidofludimus; DNA polymerase inhibitors, such as valganciclovir; EGFR family tyrosine kinase receptor modulators, such as neuregulin 4 (Crohn's disease/ulcerative colitis/necrotizing enterocolitis), Avexegen

5 Therapeutics/Children's Hospital of Los Angeles; Eosinophil peroxidase inhibitors, such as AWEPOPD-01, AWEPO-003; Eotaxin ligand inhibitors, such as bertilimumab; EP4 prostanoid receptor agonists, such as KAG-308; Epidermal growth factor agonists, such as heparin-EGF-like factor, Scios Nova; Epidermal growth factor ligands, such as Hebervis; Estrogen receptor beta agonists, such as prinaberel; Factor XIII agonists, such as catridecacog; FGF-10 ligands,

10 such as repifermin; FGF2 receptor agonists, such as F2A; Fractalkine ligand inhibitors, such as E-6011; Free fatty acid receptor 2 antagonists, such as GLPG-0974; GATA 3 transcription factor inhibitors, such as SB-012; Glucagon-like peptide 2 agonists, such as teduglutide, ZP-1848, NB-1002; Glucocorticoid agonists, such as budesonide, beclomethasone dipropionate, dexamethasone sodium phosphate, AJG-511, DOR-201, D-9421-C; GM-CSF receptor agonists,

15 such as sargramostim, molgramostim follow on biologic with fosfomycin with carbapenem (intraintestinal, Crohn's disease), Reponex; G-protein coupled receptor 84 antagonists, such as GLPG-1205; Guanylate cyclase receptor agonists, such as dolcanatide, SP-333; Histamine H2 receptor antagonists, such as bismuth, Medeva; Histone acetyltransferase inhibitors, such as TIP60 inhibitors (ulcerative colitis/inflammatory bowel disease/autoimmune diseases),

20 University of Pennsylvania; Histone deacetylase inhibitors, such as givinostat; HLA class II antigen modulators, such as HLA class II protein modulators (Crohn's disease), Nextera AS; Hydrolase inhibitors, such as SC-56938; ICAM1 gene inhibitors, such as alicaforsen; ICAM-1 inhibitors, such as alicaforsen (intravenous), ISIS-2302; IL1 gene inhibitors, such as PLR-14; IL-10 agonists, such as peg-ilodecakin, AM-0010; IL10 gene stimulators, such as gene therapy

25 (IL-10), Imperial College; IL-11 agonists, such as oprelvekin, YM-294; IL-12 antagonists, such as ustekinumab, briakinumab, apilimod; IL12 gene inhibitors, such as RDP-58; IL-13 antagonists, such as tralokinumab, anrukinzumab; IL-17 antagonists, such as secukinumab, vidofludimus; IL-2 antagonists, such as daclizumab; IL-2 receptor alpha subunit inhibitors, such as basiliximab, daclizumab, BSX-003, Ro-34-7375; IL-21 antagonists, such as NN-8828, ATR-

30 107; IL-23 antagonists, such as tildrakizumab, ustekinumab, BI-655066, AMG-139, briakinumab, LY-3074828, apilimod; IL-6 antagonists, such as tocilizumab, clazakizumab, olokizumab, HMPL-004, AMG-220, FM-101; IL6 gene inhibitors, such as YSIL6-T-PS; IL-6 receptor modulators, such as tocilizumab; IL-7 antagonists, such as interleukin-7 receptor modulators (ulcerative colitis / T-cell acute lymphoblastic leukaemia), Effimune; IL-8

antagonists, such as elubrixin, clotrimazole; Immunoglobulin G1 agonists, such as HF-1020; Immunoglobulin G2 modulators, such as PF-547659; Inosine monophosphate dehydrogenase inhibitors, such as mycophenolate mofetil; Insulin sensitizers, such as elafibranor, rosiglitazone, HE-3286, EGS-21; Integrin alpha-4/beta-1 antagonists, such as natalizumab, TRK-170, 5 fimategrast; Integrin alpha-4/beta-7 antagonists, such as etrolizumab, vedolizumab, abrilumab, carotegast methyl, TRK-170, fimategrast; Integrin alpha-E antagonists, such as etrolizumab; Integrin antagonists, such as vatelizumab, ASP-2002; Integrin beta-7 antagonists, such as etrolizumab; Interferon beta ligands, such as interferon beta-1a, recombinant interferon beta-1a, Serono; Interleukin 17E ligand inhibitors, such as anti-IL-17BR humanized antibody (lung 10 fibrosis/asthma/ulcerative colitis), Medical Research Council Technology; Interleukin ligand inhibitors, such as HE-3286; Interleukin receptor 17A antagonists, such as brodalumab; Interleukin receptor 17B antagonists, such as anti-IL-17BR humanized antibody (lung fibrosis/asthma/ulcerative colitis), Medical Research Council Technology; Interleukin-1 beta ligands, such as K(D)PT, PUR-0110, HMPL-004; Interleukin-1 beta ligand modulators, such as 15 PUR-0110, HMPL-004; Interleukin-6 ligand inhibitors, such as PF-4236921; JAK tyrosine kinase inhibitors, such as tofacitinib, peficitinib; Jak1 tyrosine kinase inhibitors, such as ABT-494, tofacitinib, filgotinib, peficitinib, GLPG-0555, solcitinib; JAK2 gene inhibitors, such as vidofludimus; Jak3 tyrosine kinase inhibitors, such as tofacitinib, peficitinib; Jun N terminal kinase inhibitors, such as semapimod; LanC like protein 2 modulators, such as BT-11; 20 Leukotriene BLT receptor antagonists, such as ONO-4057, etalocib, SC-53228, SC-52798; Lipoxigenase modulators, such as mesalazine; L-Selectin antagonists, such as BNP-001; MAdCAM inhibitors, such as vedolizumab, PF-547659; Matrix metalloprotease inhibitors, such as D-5410; Matrix metalloprotease modulators, such as D-5410; Melanocortin agonists, such as ASP-3291; Membrane copper amine oxidase inhibitors, such as vepalimomab; Metalloprotease- 25 2 inhibitors, such as KD-018, RWJ-68354; Metalloprotease-9 inhibitors, such as GS-5745; MIP 3 alpha ligand inhibitors, such as GSK-3050002; Mitochondrial 10 kDa heat shock protein stimulators, such as INV-103; Monocyte differentiation antigen CD14 inhibitors, such as CD14 anti-inflammatory, Cornell; mTOR inhibitors, such as P-2281; Mucin stimulators, such as rebamipide; NAD-dependent deacetylase sirtuin-1 stimulators, such as SRT-2104; Natriuretic peptide receptor C agonists, such as plecanatide; Neuregulin-4 ligands, such as neuregulin 4 30 (Crohn's disease/ulcerative colitis/necrotizing enterocolitis), Avexegen Therapeutics/Children's Hospital of Los Angeles; Nicotinic acetylcholine receptor agonists, such as TC-2403, nicotine polacrilex, nicotine; Nicotinic ACh receptor alpha 4 subunit modulators, such as TC-2403; Nicotinic ACh receptor alpha 7 subunit stimulators, such as GTS-21; Nicotinic ACh receptor

beta 2 subunit modulators, such as TC-2403; NK1 receptor antagonists, such as KD-018,  
 nelpitantium besilate; NKG2 D activating NK receptor antagonists, such as NNC-0142-002;  
 Nuclear factor kappa B inhibitors, such as KD-018, cobitolimod, CSA-13, HE-3286, HMPL-  
 004, Avrina, mesalamine with N-acetylcysteine, P-54; Opioid growth factor receptor agonists,  
 5 such as metenkefalin acetate with tridecactide acetate, FAR-404; Opioid receptor antagonists,  
 such as naltrexone, IRT-103; Opioid receptor delta antagonists, such as KD-018;  
 Oxidoreductase inhibitors, such as olsalazine; P2X7 purinoceptor agonists, such as givinostat;  
 p38 MAP kinase inhibitors, such as RDP-58, doramapimod, semapimod, RWJ-68354; PARP  
 inhibitors, such as EB-47, INO-1003; PDE 4 inhibitors, such as apremilast, tetomilast, CC-1088;  
 10 PDGF receptor agonists, such as oprelvekin, YM-294; Phagocytosis stimulating peptide  
 modulators, such as <sup>99m</sup>Tc-RP-128; Phospho MurNAc pentapeptide transferase inhibitors, such  
 as SQ-641; Phospholipase A2 inhibitors, such as varespladib methyl; Platelet activating factor  
 receptor antagonists, such as dersalazine sodium; Potassium channel inhibitors, such as  
 clotrimazole; PPAR alpha agonists, such as elafibranor (GFT-1007); PPAR delta agonists, such  
 15 as elafibranor (GFT-1007); PPAR gamma agonists, such as rosiglitazone, GED-0507-34-Levo,  
 etalocib; Protein CYR61 stimulators, such as CSA-13; Protein fimH inhibitors, such as EB-  
 8018; Protein kinase C alpha inhibitors, such as sotrastaurin (AEB-071); Protein kinase C beta  
 inhibitors, such as sotrastaurin (AEB-071); Protein kinase C delta inhibitors, such as sotrastaurin  
 (AEB-071); Protein kinase C epsilon inhibitors, such as sotrastaurin (AEB-071); Protein kinase  
 20 C eta inhibitors, such as sotrastaurin (AEB-071); Protein kinase C theta inhibitors, such as  
 sotrastaurin (AEB-071); Protein kinase G inhibitors, such as CEL-031; Protein kinase inhibitors,  
 such as TOP-1288; P-selectin glycoprotein ligand-1 inhibitors, such as SEL-K2; PurH purine  
 biosynthesis protein inhibitors, such as mycophenolate mofetil; Retinoic acid receptor alpha  
 agonists, such as tamibarotene; Retinoic acid receptor beta agonists, such as tamibarotene;  
 25 Retinoid receptor agonists, such as tamibarotene; RNA polymerase inhibitors, such as rifaximin;  
 SMAD-7 inhibitors, such as mongersen (GED-0301); Sodium channel inhibitors, such as  
 ropivacaine; Somatostatin receptor agonists, such as vapreotide; Sphingosine 1 phosphate  
 phosphatase 1 stimulators, such as APD-334; Sphingosine 1 phosphate phosphatase modulators,  
 such as S1P modulators (oral, multiple sclerosis/ ulcerative colitis/rheumatoid arthritis), Akaal  
 30 Pharma; Sphingosine kinase 1 inhibitors, such as ABC-294640; Sphingosine kinase 2 inhibitors,  
 such as ABC-294640; Sphingosine-1-phosphate receptor-1 agonists, such as ozanimod (RPC-  
 1063), KRP-203; Sphingosine-1-phosphate receptor-1 antagonists, such as amiselimod (MT-  
 1303); Sphingosine-1-phosphate receptor-1 modulators, such as fingolimod (FTY-720),  
 ozanimod (RPC-1063), amiselimod (MT-1303); Sphingosine-1-phosphate receptor-5

modulators, such as ozanimod; STAT3 gene inhibitors, such as vidofludimus; STAT-3 inhibitors, such as TAK-114; STAT-4 inhibitors, such as STAT-4 antisense oligonucleotide (Crohns disease/colitis), NIAID; Stem cell antigen-1 inhibitors, such as Ampion, DMI-9523; Superoxide dismutase modulators, such as midismase, LT-0011; Superoxide dismutase  
5 stimulators, such as superoxide dismutase; T cell surface glycoprotein CD28 inhibitors, such as abatacept; TGF beta 1 ligand inhibitors, such as mongersen, GED-0301; Thymulin agonists, such as Syn-1002; TLR-2 antagonists, such as VB-201; TLR-4 antagonists, such as JKB-122, VB-201; TLR-9 agonists, such as BL-7040, cobitolimod; TNF alpha ligand inhibitors, such as adalimumab, certolizumab pegol, infliximab biosimilar, infliximab, golimumab, ISIS-104838,  
10 CSA-13, DLX-105, adalimumab biosimilar, dersalazine sodium, Debio-0512, HMPL-004, DLX-105, infliximab follow-on biologic, AZD-9773, CYT-020-TNFQb, DOM-0200; TNF alpha ligand modulators, such as PUR-0110, CDP-571; TNF antagonists, such as etanercept, certolizumab pegol, AVX-470, onercept; Trefoil factor modulators, such as AG-012; Tryptase inhibitors, such as APC-2059; Tryptophan 5-hydroxylase inhibitors, such as telotristat etiprate;  
15 Tumor necrosis factor 14 ligand modulators, such as SAR-252067; Type I TNF receptor antagonists, such as DOM-0100; Type II TNF receptor modulators, such as etanercept; Unspecified growth factor receptor modulators, such as AP-005; Vanilloid VR1 agonists, such as zucapsaicin; Vitamin D3 receptor agonists, such as calcitriol; and Zonulin inhibitors, such as larazotide acetate, AT-1001.

20 Also, the following non-exhaustive list of classes of compounds and compounds may be combined with a compound of the present disclosure: 14-3-3 protein eta inhibitors, 5-Lipoxygenase inhibitors, Abl tyrosine kinase inhibitors, ACTH receptor agonists, Adenosine A3 receptor agonists, Adenosine deaminase inhibitors, ADP ribosyl cyclase-1 modulators, ADP ribosylation factor 6 inhibitors, Adrenocorticotrophic hormone ligands, Aggrecanase-2  
25 inhibitors, Albumin modulators, AP1 transcription factor inhibitors, Basigin inhibitors, Bcr protein inhibitors, B-lymphocyte antigen CD19 inhibitors, B-lymphocyte antigen CD20 inhibitors, B-lymphocyte antigen CD20 modulators, B-lymphocyte stimulator ligand inhibitors, Bradykinin receptor modulators, BRAF gene inhibitors, Branched amino acid aminotransferase  
30 1 inhibitors, Bromodomain containing protein inhibitors, Btk tyrosine kinase inhibitors, Cadherin-11 antagonists, Calcineurin inhibitors, Calcium channel inhibitors, Carbonic anhydrase inhibitors, Cathepsin K inhibitors, Cathepsin S inhibitors, CCR1 chemokine antagonists, CCR2 chemokine antagonists, CCR3 gene modulators, CCR5 chemokine antagonists, CD126 antagonists, CD29 modulators, CD3 modulators, CD39 agonists, CD4 agonists, CD4 antagonists, CD40 ligand inhibitors, CD40 ligand receptor antagonists, CD40 ligand receptor

modulators, CD52 antagonists, CD73 agonists, CD79b modulators, CD80 antagonists, CD86  
 antagonists, CD95 antagonists, Cell adhesion molecule inhibitors, Choline kinase inhibitors,  
 Clusterin stimulators, Complement C5 factor inhibitors, Complement Factor stimulators, C-  
 reactive protein inhibitors, CSF-1 antagonists, CXC10 chemokine ligand inhibitors, CXCR4  
 5 chemokine antagonists, Cyclin-dependent kinase inhibitor 1 inhibitors, Cyclin-dependent  
 kinase-2 inhibitors, Cyclin-dependent kinase-4 inhibitors, Cyclin-dependent kinase-5 inhibitors,  
 Cyclin-dependent kinase-6 inhibitors, Cyclin-dependent kinase-7 inhibitors, Cyclin-dependent  
 kinase-9 inhibitors, Cyclooxygenase 2 inhibitors, Cyclooxygenase 2 modulators,  
 Cyclooxygenase inhibitors, Cytosolic phospholipase A2 inhibitors, Cytotoxic T-lymphocyte  
 10 protein-4 modulators, Cytotoxic T-lymphocyte protein-4 stimulators, DHFR inhibitors, Diamine  
 acetyltransferase inhibitors, Dihydroorotate dehydrogenase inhibitors, Elongation factor 2  
 inhibitors, Eotaxin 2 ligand inhibitors, EP4 prostanoid receptor antagonists, Erythropoietin  
 receptor agonists, Fas ligands, FGF-2 ligand inhibitors, FK506 binding protein-12 modulators,  
 Folate antagonists, Folate receptor agonists, Folate receptor beta antagonists, Folate receptor  
 15 modulators, Fractalkine ligand inhibitors, Fyn tyrosine kinase inhibitors, G protein coupled  
 receptor 15 antagonists, GABA A receptor modulators, Glucocorticoid agonists, Glucocorticoid  
 antagonists, Glucocorticoid induced leucine zipper stimulators, GM-CSF ligand inhibitors, GM-  
 CSF receptor antagonists, GM-CSF receptor modulators, Growth regulated protein alpha ligand  
 inhibitors, Hwith Kwith ATPase inhibitors, Histamine H4 receptor antagonists, Histone  
 20 deacetylase inhibitors, Histone deacetylase-6 inhibitors, HIV-1 gp120 protein inhibitors, HLA  
 class II antigen DQ-2 alpha modulators, HLA class II antigen inhibitors, HLA class II antigen  
 modulators, Hsp 70 family inhibitors, Hypoxia inducible factor-1 inhibitors, IFNB gene  
 stimulators, I-kappa B kinase beta inhibitors, I-kappa B kinase inhibitors, IL-1 antagonists, IL-  
 10 agonists, IL-11 agonists, IL-12 antagonists, IL-15 antagonists, IL-17 antagonists, IL-17  
 25 receptor modulators, IL-2 agonists, IL-2 antagonists, IL-21 antagonists, IL-23 antagonists, IL-3  
 antagonists, IL-4 agonists, IL-6 antagonists, IL-6 receptor modulators, Immunoglobulin  
 antagonists, Immunoglobulin G1 agonists, Immunoglobulin G1 antagonists, Immunoglobulin  
 G1 modulators, Immunoglobulin G2 antagonists, Immunoglobulin G2 modulators,  
 Immunoglobulin gamma Fc receptor II modulators, Immunoglobulin gamma Fc receptor IIB  
 30 antagonists, Immunoglobulin kappa modulators, Immunoglobulin M antagonists, Inducible  
 nitric oxide synthase inhibitors, Inosine monophosphate dehydrogenase inhibitors, Insulin  
 sensitizers, Integrin alpha-1/beta-1 antagonists, Integrin alpha-4/beta-1 antagonists, Integrin  
 antagonists, Interferon beta ligands, Interferon gamma ligands, Interleukin 17A ligand  
 inhibitors, Interleukin 17F ligand inhibitors, Interleukin 23A inhibitors, Interleukin ligands,

Interleukin receptor 17A antagonists, Interleukin-1 beta ligand inhibitors, Interleukin-10 ligands, Interleukin-2 ligands, Interleukin-4 ligands, Interleukin-6 ligand inhibitors, Itk tyrosine kinase inhibitors, JAK tyrosine kinase inhibitors, Jak1 tyrosine kinase inhibitors, Jak2 tyrosine kinase inhibitors, JAK3 gene inhibitors, Jak3 tyrosine kinase inhibitors, Jun N terminal kinase inhibitors, KCNA voltage-gated potassium channel-3 modulators, Kelch like ECH associated protein 1 modulators, Kit tyrosine kinase inhibitors, LanC like protein 2 modulators, LITAF gene inhibitors, Lymphocyte function antigen-3 receptor antagonists, Lyn tyrosine kinase inhibitors, Macrophage mannose receptor 1 modulators, MAdCAM inhibitors, MAP kinase modulators, MAP3K2 gene inhibitors, MAPKAPK5 inhibitors, Matrix metalloprotease inhibitors, MCL1 gene inhibitors, MEK protein kinase inhibitors, MEK-1 protein kinase inhibitors, MEK-2 protein kinase inhibitors, Membrane copper amine oxidase inhibitors, Metalloprotease-2 inhibitors, Metalloprotease-9 inhibitors, Midkine ligand inhibitors, Mitochondrial 10 kDa heat shock protein stimulators, mTOR complex 1 inhibitors, mTOR inhibitors, NAD ADP ribosyltransferase stimulators, NAMPT gene inhibitors, NF kappa B inhibitor stimulators, NFAT gene inhibitors, NFE2L2 gene stimulators, Nicotinic acetylcholine receptor antagonists, NK cell receptor modulators, NKG2 A B activating NK receptor antagonists, NKG2 D activating NK receptor antagonists, Nuclear erythroid 2-related factor 2 stimulators, Nuclear factor kappa B inhibitors, Nuclear factor kappa B modulators, Nuclear factor kappa B p105 inhibitors, Opioid growth factor receptor agonists, Opioid receptor delta antagonists, Osteoclast differentiation factor antagonists, Osteoclast differentiation factor ligand inhibitors, Oxidoreductase inhibitors, P2X7 purinoceptor agonists, p38 MAP kinase alpha inhibitors, p38 MAP kinase inhibitors, PDE 4 inhibitors, PDE 5 inhibitors, PDGF receptor agonists, PDGF receptor antagonists, PDGF-B ligand inhibitors, PERK gene inhibitors, Phosphoinositide-3 kinase delta inhibitors, Phosphoinositide-3 kinase gamma inhibitors, Phospholipase A2 inhibitors, Platelet activating factor receptor antagonists, PPAR gamma agonists, Programmed cell death protein 1 modulators, Prostaglandin D synthase stimulators, Protein arginine deiminase inhibitors, Protein tyrosine kinase inhibitors, PurH purine biosynthesis protein inhibitors, Rho associated protein kinase 2 inhibitors, Seprase inhibitors, Signal transducer CD24 modulators, Signal transduction inhibitors, Sodium glucose transporter-2 inhibitors, Sphingosine 1 phosphate phosphatase modulators, STAT3 gene inhibitors, Superoxide dismutase stimulators, SYK family tyrosine kinase inhibitors, Syk tyrosine kinase inhibitors, Syndecan-1 inhibitors, T cell receptor antagonists, T cell receptor modulators, T cell surface glycoprotein CD28 inhibitors, T cell surface glycoprotein CD28 stimulators, TAK1 binding protein modulators, Talin modulators, T-cell differentiation antigen CD6 inhibitors, T-

cell surface glycoprotein CD8 inhibitors, Tenascin modulators, TGF beta agonists, Thymulin  
 agonists, TLR-2 antagonists, TLR-4 antagonists, TLR-9 antagonists, TNF alpha ligand  
 inhibitors, TNF alpha ligand modulators, TNF antagonists, TNF gene inhibitors, TNF receptor  
 modulators, TNFSF11 gene inhibitors, Transcription factor p65 inhibitors, Transcription factor  
 5 RelB inhibitors, Transferrin modulators, Tumor necrosis factor 13C receptor antagonists, Tumor  
 necrosis factor 15 ligand inhibitors, Tumor necrosis factor ligand 13 inhibitors, Tumor necrosis  
 factor ligand inhibitors, Type I IL-1 receptor antagonists, Type I TNF receptor antagonists, Type  
 II TNF receptor modulators, Unspecified GPCR agonists, VEGF receptor antagonists, VEGF-2  
 receptor antagonists, VEGF-2 receptor modulators, VEGF-B ligand inhibitors, X-linked  
 10 inhibitor of apoptosis protein inhibitors, Zap70 tyrosine kinase inhibitors, 99mTc labelled  
 annexin V-128, abatacept, abatacept biosimilar, ABBV-257, ABT-122, ABT-494, acalabrutinib,  
 aceclofenac, actarit, MS-392, adalimumab, adalimumab biosimilar, adalimumab follow-on  
 biologic, AK-106, ALX-0061, aminopterin, anakinra, anakinra biosimilar, anakinra follow-on  
 biologic, ARG-301, ASLAN-003, ASP-5094, AT-132, AZD-9567, baricitinib, BI-655064,  
 15 bimekizumab, BiP (rheumatoid arthritis), Kings College London, BLHP-006, blisibimod, BMS-  
 986104, BMS-986142, ABBV-105, BTT-1023, canakinumab, Cartistem, CCX-354, CD24-IgFc,  
 celecoxib, cerdulatinib, certolizumab pegol, CF-101, CFZ-533, CHR-5154, cibinetide,  
 ciclosporin, clazakizumab, CNTO-6785, corticotropin, Mallinckrodt, CR-6086, CreaVax-RA,  
 CWG-92, CWG-940, Cx-611, DE-098, deflazacort, Rheumavax, denosumab, diacerein,  
 20 diclofenac, E-6011, eicosapentaenoic acid monoglycerides, etanercept, etanercept biosimilar,  
 etanercept follow-on biologic, etodolac, etoricoxib, filgotinib, fosdagrocorat, gerilimzumab,  
 ginsenoside C-K, givinostat, goat polyclonal antibodies, golimumab, GS-5745, GS-9876, GSK-  
 3196165, HM-71224, HMPL-523, hyaluronate sodium, IB-RA (injectable, rheumatoid arthritis),  
 Innobioscience, IB-RA (oral, rheumatoid arthritis), Innobioscience, iguratimod, IMD-2560,  
 25 imidazole salicylate, infliximab, infliximab biobetter, infliximab biosimilar, INSIX RA,  
 interferon gamma follow-on biologic, interleukin-2 (injectable), interleukin-2 follow-on  
 biologic, INV-103, IR-501, itolizumab, JNJ-40346527, Ka Shu Ning, KD-025, ketoprofen with  
 omeprazole, leflunomide, lenzilumab, LLDT-8, lumiracoxib, LY-3090106, masitinib,  
 mavrilimumab, MBS-2320, MEDI-5117, meloxicam, methotrexate, MGD-010, misoprostol with  
 30 diclofenac, MM-A01-01, monalizumab, MORAb-022, MPC-300-IV, MRC-375, nabumetone,  
 namilumab, naproxen with esomeprazole, naproxen with esomeprazole strontium,  
 ocaratuzumab, ofatumumab, OHR-118 , olokizumab, OM-89, once-daily naproxen (oral  
 controlled release, pain), Alvogen, ONO-4059, Oralgam, ozoralizumab, peficitinib,  
 pelubiprofen, PF-06687234, piperidone hydrochloridum, piroxicam, prednisolone, prednisone,

Prosorba, PRT-2607, PRTX-100, PRX-167700, QBSAU, rabeximod, RCT-18, recombinant human CD22 monoclonal antibody (iv infusion), Lonn Ryonn Pharma/SinoMab Bioscience (Shenzhen), recombinant human interleukin-1 receptor antagonist (rheumatoid arthritis), Shanghai Fudan-Zhangjiang Bio-Pharmaceutical, recombinant human interleukin-2 recombinant

5 TNF receptor 2-Fc fusion protein mutant , RG-6125, RhuDex, rifabutin with clarithromycin with clofazimine, rituximab, rituximab biosimilar, rituximab follow-on biologic, RPI-78, SAN-300, sarilumab, SBI-087, seliciclib, SHR-0302, sirukumab, spebrutinib, SSS-07, KDDF-201110-06, Syn-1002, T-5224, TAB-08, tacrolimus, TAK-020, TAK-079, tarenflurbil (transdermal spraygel, skin disease/rheumatoid arthritis), MIKA Pharma/GALENpharma, technetium Tc 99m

10 tilmanocept, technetium[99Tc] methylenediphosphonate, tenoxicam, Debio-0512, tocilizumab, tofacitinib, Trichuris suis ova, umbilical cord-derived mesenchymal stem cells (iv, RA/liver disease), Alliancells/Zhongyuan Union, ustekinumab, VAY-736, VB-201, WF-10, XmAb-5871, YHB-1411-2; 14-3-3 protein eta inhibitors, such as anti-AGX-020 mAbs (rheumatoid arthritis), Augurex; 5-Lipoxygenase inhibitors, such as tenoxicam, darbufelone, tebufelone, licofelone,

15 ZD-2138, etalocib, tenidap, tepoxalin, flobufen, SKF-86002, PGV-20229, L-708780, WY-28342, T-0757, T-0799, ZM-216800, L-699333, BU-4601A, SKF-104351, CI-986; Abl tyrosine kinase inhibitors, such as imatinib; ACTH receptor agonists, such as FAR-404, metenkefalin acetate with tridecactide acetate; Adenosine A3 receptor agonists, such as CF-101; Adenosine deaminase inhibitors, such as cladribine, pentostatin, FR-221647; ADP ribosyl cyclase-1

20 modulators, such as indatuximab ravtansine; ADP ribosylation factor 6 inhibitors, such as NAV-2729; Adrenocorticotrophic hormone ligands, such as corticotropin, Mallinckrodt, FAR-404, metenkefalin acetate with tridecactide acetate; Aggrecanase-2 inhibitors, such as GIBH-R-001-2; Albumin modulators, such as ALX-0061, ONS-1210; AP1 transcription factor inhibitors, such as T-5224, tarenflurbil, SP-10030; Basigin inhibitors, such as ERG-240; Bcr protein

25 inhibitors, such as imatinib; B-lymphocyte antigen CD19 inhibitors, such as XmAb-5871, MDX-1342; B-lymphocyte antigen CD20 inhibitors, such as ocrelizumab, ofatumumab, rituximab, rituximab biosimilar, veltuzumab, rituximab follow-on biologic, ocaratuzumab, BLX-301, IDEC-102, ABP-798, GP-2013, MK-8808, HLX-01, CT-P10, TL-011, PF-05280586, IBPM-001RX, IBI-301, AME-133v, BCD-020, BT-D004, SAIT-101; B-lymphocyte antigen

30 CD20 modulators, such as rituximab biosimilar, SBI-087, TRU-015, DXL-625; B-lymphocyte stimulator ligand inhibitors, such as belimumab, RCT-18, blisibimod, tabalumab, atacicept, briobacept; Bradykinin receptor modulators, such as givinostat; BRAF gene inhibitors, such as binimetinib; Branched amino acid aminotransferase 1 inhibitors, such as ERG-240; Bromodomain containing protein inhibitors, such as RVX-297, ZEN-003694; Btk tyrosine

kinase inhibitors, such as acalabrutinib, HM-71224, spebrutinib, BTK inhibitor (rheumatoid arthritis), Humanwell Healthcare/Wuxi AppTech, BMS-986142, TAK-020, ONO-4059, TAS-5315, ABBV-105, AC-0025, RN-486, CG-026806, GDC-0834; Cadherin-11 antagonists, such as RG-6125; Calcineurin inhibitors, such as HS-378, ciclosporin; Calcium channel inhibitors, such as RP-3128; Carbonic anhydrase inhibitors, such as polmacoxib; Cathepsin K inhibitors, such as CRA-013783, T-5224, AM-3876, VEL-0230, NPI-2019; Cathepsin S inhibitors, such as MIV-247, AM-3876, RWJ-445380, NPI-2019; CCR1 chemokine antagonists, such as BX-471, BMS-817399, BI-638683, CCX-354, MLN-3701, MLN-3897, CP-481715, PS-375179; CCR2 chemokine antagonists, such as MK-0812, AZD-6942; CCR3 gene modulators, such as CM-102; CCR5 chemokine antagonists, such as maraviroc, OHR-118, NIBR-6465, AZD-5672, AZD-8566; CD126 antagonists, such as sarilumab; CD29 modulators, such as PF-06687234; CD3 modulators, such as oteeliximumab; CD39 agonists, such as AAV5-CD39/CD73 (rheumatoid arthritis), Arthrogen; CD4 agonists, such as maraviroc; CD4 antagonists, such as tregalizumab, zanolimumab, MTRX-1011A, BW-4162W94, EP-1645, clenoliximab; CD40 ligand inhibitors, such as dapirolizumab pegol; CD40 ligand receptor antagonists, such as BI-655064, anti-CD40-XTEN, teneliximab; CD40 ligand receptor modulators, such as CFZ-533; CD52 antagonists, such as alemtuzumab; CD73 agonists, such as AAV5-CD39/CD73 (rheumatoid arthritis), Arthrogen; CD79b modulators, such as MGD-010; CD80 antagonists, such as RhuDex, XENP-9523, ASP-2408, abatacept biobetter; CD86 antagonists, such as ES-210, abatacept biosuperior, ASP-2408, XENP-9523; CD95 antagonists, such as DE-098, CS-9507; Cell adhesion molecule inhibitors, such as natalizumab, alicaforsen, NPC-17923, TK-280, PD-144795; Choline kinase inhibitors, such as choline kinase inhibitors (rheumatoid arthritis), UC San Diego; Clusterin stimulators, such as alemtuzumab; Complement C5 factor inhibitors, such as eculizumab, antisense oligonucleotides (rheumatoid arthritis), Leiden University Medical Center; Complement Factor stimulators, such as CM-101; C-reactive protein inhibitors, such as IB-RA (oral, rheumatoid arthritis), Innobioscience, ISIS-353512; CSF-1 antagonists, such as masitinib, FPA-008, JNJ-27301937, JNJ-40346527, PLX-5622, CT-1578, PD-360324, JNJ-28312141; CXC10 chemokine ligand inhibitors, such as 946414-98-8, BMS-936557; CXCR4 chemokine antagonists, such as plerixafor; Cyclin-dependent kinase inhibitor 1 inhibitors, such as CDK-1/2/5/7/9 inhibitors (cancer/tumorogenesis/rheumatoid arthritis), BioPatterns; Cyclin-dependent kinase-2 inhibitors, such as seliciclib, BP-14; Cyclin-dependent kinase-4 inhibitors, such as CDK-4/6 inhibitor (rheumatoid arthritis), Teijin; Cyclin-dependent kinase-5 inhibitors, such as BP-14; Cyclin-dependent kinase-6 inhibitors, such as CDK-4/6 inhibitor (rheumatoid arthritis), Teijin; Cyclin-dependent kinase-7 inhibitors, such as BP-14,

seliciclib; Cyclin-dependent kinase-9 inhibitors, such as BP-14, seliciclib; Cyclooxygenase 2 inhibitors, such as celecoxib, etoricoxib, polmacoxib, laflunimus, etodolac, meloxicam, IB-RA (injectable, rheumatoid arthritis), Innobioscience, IB-RA (oral, rheumatoid arthritis), Innobioscience, SKLB-023, meloxicam, lumiracoxib; Cyclooxygenase 2 modulators, such as DRGT-46; Cyclooxygenase inhibitors, such as aceclofenac, diclofenac, imidazole salicylate, naproxcinod, naproxen etemesil, misoprostol with diclofenac, nabumetone, naproxen with esomeprazole, naproxen with esomeprazole strontium, once-daily naproxen (oral controlled release, pain), Alvogen, pelubiprofen, LY-210073, tenoxicam, licofelone, NS-398, bromfenac, L-746483, LY-255283, tenidap, tepoxalin, flobufen, ibuprofen, flurbiprofen, SKF-86002, SC-57666, WY-28342, CI-986, bermoprofen; Cytosolic phospholipase A2 inhibitors, such as AVX-002; Cytotoxic T-lymphocyte protein-4 modulators, such as belatacept, ES-210; Cytotoxic T-lymphocyte protein-4 stimulators, such as abatacept, abatacept biosimilar, BMS-188667; DHFR inhibitors, such as methotrexate, MPI-2505, MBP-Y003; Diamine acetyltransferase inhibitors, such as diminazene aceturate; Dihydroorotate dehydrogenase inhibitors, such as DHODH inhibitors (rheumatoid arthritis/autoimmune diseases), East China University of Science and Technology, ASLAN-003, laflunimus, leflunomide, HWA-486, ABR-224050; Elongation factor 2 inhibitors, such as denileukin diftitox; Eotaxin 2 ligand inhibitors, such as CM-102; EP4 prostanoid receptor antagonists, such as CR-6086; Erythropoietin receptor agonists, such as cibinetide; Fas ligands, such as AP-300; FGF-2 ligand inhibitors, such as RBM-007; FK506 binding protein-12 modulators, such as temsirolimus; Folate antagonists, such as methotrexate, MBP-Y003; Folate receptor agonists, such as folate receptor modulators (chimeric protein, cancer/rheumatoid arthritis), Proda Biotech; Folate receptor modulators, such as technetium (99mTc) etarfolatide; Fractalkine ligand inhibitors, such as E-6011; Fyn tyrosine kinase inhibitors, such as masitinib, laflunimus; G protein coupled receptor 15 antagonists, such as GPR15 antagonists (rheumatoid arthritis/HIV-mediated enteropathy), Omeros; GABA A receptor modulators, such as laflunimus; Glucocorticoid agonists, such as prednisolone, fosdagrocorat; Glucocorticoid antagonists, such as REC-200; Glucocorticoid induced leucine zipper stimulators, such as ART-G01; GM-CSF ligand inhibitors, such as namilumab, MORAb-022, lenzilumab; GM-CSF receptor antagonists, such as mavrilimumab; GM-CSF receptor modulators, such as GSK-3196165; Growth regulated protein alpha ligand inhibitors, such as T-5224; Hwith Kwith ATPase inhibitors, such as naproxen with esomeprazole, naproxen with esomeprazole strontium, ketoprofen with omeprazole, KEO-25001, HC-1004, PN-40020; Histamine H4 receptor antagonists, such as toreforant, GD-48; Histone deacetylase inhibitors, such as givinostat, CHR-5154; Histone deacetylase-6 inhibitors, such as CKD-506; HIV-1

gp120 protein inhibitors, such as maraviroc; HLA class II antigen DQ-2 alpha modulators, such as NexVax2; HLA class II antigen inhibitors, such as HLA-DR1/DR4 inhibitors (rheumatoid arthritis), Provid; HLA class II antigen modulators, such as ARG-301, recombinant T-cell receptor ligand (rheumatoid arthritis), Artielle; Hsp 70 family inhibitors, such as gusperimus trihydrochloride; Hypoxia inducible factor-1 inhibitors, such as 2-methoxyestradiol; IFNB gene stimulators, such as ART-102; I-kappa B kinase beta inhibitors, such as IMD-2560, IMD-0560; I-kappa B kinase inhibitors, such as bardoxolone methyl; IL-1 antagonists, such as riloncept, IBPB-007-IL, antisense oligonucleotides (rheumatoid arthritis), Leiden University Medical Center, recombinant human interleukin-1 receptor antagonist (rheumatoid arthritis), Shanghai Fudan-Zhangjiang Bio-Pharmaceutical; IL-10 agonists, such as peg-ilodecakin; IL-11 agonists, such as oprelvekin; IL-12 antagonists, such as ustekinumab, briakinumab, ddRNAi therapy (rheumatoid arthritis), Medistem/Benitec; IL-15 antagonists, such as AMG-714, BNZ-132-2; IL-17 antagonists, such as ixekizumab, secukinumab, KD-025; IL-17 receptor modulators, such as CNTO-6785; IL-2 agonists, such as interleukin-2 follow-on biologic; IL-2 antagonists, such as IB-RA (injectable, rheumatoid arthritis), Innobioscience, IB-RA (oral, rheumatoid arthritis), Innobioscience, BNZ-132-2; IL-21 antagonists, such as NN-8828, BNZ-132-2; IL-23 antagonists, such as ustekinumab, briakinumab; IL-3 antagonists, such as anti-IL-3 mAbs (rheumatoid arthritis), University of Regensburg; IL-4 agonists, such as SER-130-AMI; IL-6 antagonists, such as olokizumab, clazakizumab, sirukumab, SA-237, tocilizumab, ALX-0061, FB-704A, OP-R003, peptide IL-6 antagonist, MEDI-5117, T-5224, humanized anti-IL-6 mAb, tocilizumab biosimilar, IL-6 neutralizing human antibodies, anti-IL6 antibody, RN-486, BLX-1002, AMG-220, FM-101, K-832, BLX-1025, esonarimod, TA-383; IL-6 receptor modulators, such as tocilizumab, tocilizumab biosimilar, RO-4877533; Immunoglobulin antagonists, such as iguratimod; Immunoglobulin G1 agonists, such as canakinumab, infliximab biobetter, infliximab biosimilar, BX-2922, STI-002, HF-1020; Immunoglobulin G1 antagonists, such as YHB-1411-2; Immunoglobulin G1 modulators, such as CFZ-533, lenzilumab; Immunoglobulin G2 antagonists, such as denosumab; Immunoglobulin G2 modulators, such as PF-547659; Immunoglobulin gamma Fc receptor II modulators, such as MGD-010; Immunoglobulin gamma Fc receptor IIB antagonists, such as XmAb-5871; Immunoglobulin kappa modulators, such as lenzilumab; Immunoglobulin M antagonists, such as IB-RA (injectable, rheumatoid arthritis), Innobioscience, IB-RA (oral, rheumatoid arthritis), Innobioscience; Inducible nitric oxide synthase inhibitors, such as SKLB-023; Inosine monophosphate dehydrogenase inhibitors, such as mycophenolate mofetil; Insulin sensitizers, such as rosiglitazone, THR-0921, HE-3286, BLX-1002; Integrin alpha-1/beta-1 antagonists, such as SAN-300; Integrin alpha-4/beta-1 antagonists,

such as natalizumab; Integrin antagonists, such as PEG-HM-3, CY-9652; Interferon beta ligands, such as recombinant interferon beta-1a, TA-383; Interferon gamma ligands, such as interferon gamma follow-on biologic; Interleukin 17A ligand inhibitors, such as ABT-122, bimekizumab, ABBV-257; Interleukin 17F ligand inhibitors, such as bimekizumab; Interleukin

5 23A inhibitors, such as guselkumab; Interleukin ligands, such as IBPB-007-IL; Interleukin receptor 17A antagonists, such as brodalumab; Interleukin-1 beta ligand inhibitors, such as canakinumab, riloncept, T-5224, gevokizumab, BLX-1002, LY-2189102, PMI-001, K-832, CDP-484; Interleukin-10 ligands, such as PF-06687234; Interleukin-2 ligands, such as denileukin diftitox, recombinant interleukin-2, interleukin-2 follow-on biologic, recombinant

10 human interleukin-2, interleukin-2 (injectable); Interleukin-4 ligands, such as Tetravil; Interleukin-6 ligand inhibitors, such as gerilimzumab, PF-4236921; Itk tyrosine kinase inhibitors, such as ARN-4079; JAK tyrosine kinase inhibitors, such as tofacitinib, SHR-0302, cerdulatinib, peficitinib, deuterated tofacitinib analog, SD-900, CVXL-0074; Jak1 tyrosine kinase inhibitors, such as ABT-494, baricitinib, ruxolitinib, filgotinib, tofacitinib, itacitinib,

15 peficitinib, NIP-585, CS-944X, YJC-50018, GLPG-0555, MRK-12; Jak2 tyrosine kinase inhibitors, such as baricitinib, ruxolitinib, CT-1578; JAK3 gene inhibitors, such as GBL-5b; Jak3 tyrosine kinase inhibitors, such as decernotinib, tofacitinib, peficitinib, AC-0025, CS-944X, DNX-04042, MTF-003, ARN-4079, PS-020613; Jun N terminal kinase inhibitors, such as IQ-1S; KCNA voltage-gated potassium channel-3 modulators, such as MRAD-P1; Kelch like

20 ECH associated protein 1 modulators, such as dimethyl fumarate; Kit tyrosine kinase inhibitors, such as imatinib, masitinib; LanC like protein 2 modulators, such as BT-11; LITAF gene inhibitors, such as GBL-5b; Lymphocyte function antigen-3 receptor antagonists, such as alefacept; Lyn tyrosine kinase inhibitors, such as masitinib; Macrophage mannose receptor 1 modulators, such as technetium Tc 99m tilmanocept; MAdCAM inhibitors, such as PF-547659;

25 MAP kinase modulators, such as SKLB-023; MAP3K2 gene inhibitors, such as GBL-5b; MAPKAPK5 inhibitors, such as GLPG-0259; Matrix metalloprotease inhibitors, such as GLPG-0259; MCL1 gene inhibitors, such as seliciclib; MEK protein kinase inhibitors, such as binimetinib, AD-GL0001; MEK-1 protein kinase inhibitors, such as binimetinib; MEK-2 protein kinase inhibitors, such as binimetinib; Membrane copper amine oxidase inhibitors, such as BTT-

30 1023, PRX-167700, vepalimomab; Metalloprotease-2 inhibitors, such as ERG-240; Metalloprotease-9 inhibitors, such as GS-5745, ERG-240; Midkine ligand inhibitors, such as CAB-102; Mitochondrial 10 kDa heat shock protein stimulators, such as INV-103; mTOR complex 1 inhibitors, such as everolimus; mTOR inhibitors, such as everolimus, temsirolimus; NAD ADP ribosyltransferase stimulators, such as denileukin diftitox; NAMPT gene inhibitors,

such as ART-D01; NF kappa B inhibitor stimulators, such as denosumab; NFAT gene inhibitors, such as T-5224; NFE2L2 gene stimulators, such as bardoxolone methyl; Nicotinic acetylcholine receptor antagonists, such as RPI-78, RPI-MN; NK cell receptor modulators, such as masitinib; NKG2 A B activating NK receptor antagonists, such as monalizumab; NKG2 D activating NK receptor antagonists, such as NNC-0142-002; Nuclear erythroid 2-related factor 2 stimulators, 5 such as dimethyl fumarate; Nuclear factor kappa B inhibitors, such as bardoxolone methyl, IB-RA (injectable, rheumatoid arthritis), Innobioscience, dehydroxymethylepoxyquinomicin, HE-3286, IMD-0560, MP-42, tarenflurbil, VGX-1027, SKLB-023, SP-650003, MG-132, SIM-916, VGX-350, VGX-300, GIT-027, SP-100030, MLN-1145, NVP-IKK-005; Nuclear factor kappa B 10 modulators, such as REM-1086; Nuclear factor kappa B p105 inhibitors, such as REM-1086; Opioid growth factor receptor agonists, such as metenkefalin acetate with tridecactide acetate, FAR-404; Opioid receptor delta antagonists, such as HS-378; Osteoclast differentiation factor antagonists, such as denosumab, cyclic peptidomimetics (rheumatoid arthritis/osteoporosis), University of Michigan; Osteoclast differentiation factor ligand inhibitors, such as denosumab; 15 Oxidoreductase inhibitors, such as etodolac, imidazole salicylate; P2X7 purinoceptor agonists, such as givinostat; p38 MAP kinase alpha inhibitors, such as VX-745, BMS-582949 prodrugs, BMS-751324; p38 MAP kinase inhibitors, such as BCT-197, losmapimod, ARRY-797; PDE 4 inhibitors, such as apremilast; PDE 5 inhibitors, such as PDE5 inhibitors (rheumatoid arthritis), University of Rochester; PDGF receptor agonists, such as oprelvekin; PDGF receptor 20 antagonists, such as imatinib, masitinib; PDGF-B ligand inhibitors, such as SL-1026; PERK gene inhibitors, such as binimetinib; Phosphoinositide-3 kinase delta inhibitors, such as duvelisib, RP-6503, CT-732, INK-007, GNE-293; Phosphoinositide-3 kinase gamma inhibitors, such as duvelisib, RP-6503; Phospholipase A2 inhibitors, such as AVX-002, human secreted phospholipase A2 type IIA-integrin binding inhibiting peptides (rheumatoid 25 arthritis/asthma/Alzheimer's disease/cancer), University of California, Davis, AK-106, varespladib methyl, Ro-31-4493, BM-162353, Ro-23-9358, YM-26734; Platelet activating factor receptor antagonists, such as piperidone hydrochloridum; PPAR gamma agonists, such as rosiglitazone, THR-0921, rosiglitazone XR, etalocib; Programmed cell death protein 1 modulators, such as INSIX RA; Prostaglandin D synthase stimulators, such as HF-0220; Protein 30 arginine deiminase inhibitors, such as PAD inhibitors (rheumatoid arthritis), Leiden University Medical Center/LURIS; Protein tyrosine kinase inhibitors, such as leflunomide; PurH purine biosynthesis protein inhibitors, such as mycophenolate mofetil; Rho associated protein kinase 2 inhibitors, such as KD-025; Seprase inhibitors, such as anti-fibroblast-activation protein (FAP) antibody radiotracers (rheumatoid arthritis), Hoffmann-La Roche/ Radboud University; Signal

transducer CD24 modulators, such as CD24-IgFc; Signal transduction inhibitors, such as imatinib; Sodium glucose transporter-2 inhibitors, such as THR-0921; Sphingosine 1 phosphate phosphatase modulators, such as S1P modulators (oral, multiple sclerosis/ ulcerative colitis/rheumatoid arthritis), Akaal Pharma; STAT3 gene inhibitors, such as bardoxolone methyl, vidofludimus; Superoxide dismutase stimulators, such as imisopasem manganese; SYK family tyrosine kinase inhibitors, such as MK-8457; Syk tyrosine kinase inhibitors, such as fostamatinib, entospletinib, KDDF-201110-06, HMPL-523, cerdulatinib, AB-8779, GS-9876, PRT-2607, CVXL-0074, CG-103065 and CG-026806; Syndecan-1 inhibitors, such as indatuximab ravtansine; T cell receptor antagonists, such as TCR inhibiting SCHOOL peptides (systemic/topical, rheumatoid arthritis/dermatitis/scleroderma), SignaBlok, CII modified peptide (rheumatoid arthritis), Peking University; T cell receptor modulators, such as ARG-301; T cell surface glycoprotein CD28 inhibitors, such as abatacept, belatacept, abatacept biosimilar, RhuDex, BMS-188667; T cell surface glycoprotein CD28 stimulators, such as TAB-08; TAK1 binding protein modulators, such as epigallocatechin 3-gallate; Talin modulators, such as short-form talin regulators (rheumatoid arthritis), KayteeBio; T-cell differentiation antigen CD6 inhibitors, such as itolizumab; T-cell surface glycoprotein CD8 inhibitors, such as tregalizumab; Tenascin modulators, such as Tetravil; TGF beta agonists, such as tregalizumab; Thymulin agonists, such as Syn-1002; TLR-2 antagonists, such as VB-201, P-13; TLR-4 antagonists, such as VB-201, P-13; TLR-9 antagonists, such as P-13; TNF alpha ligand inhibitors, such as adalimumab biosimilar YHB-1411-2, adalimumab, infliximab, infliximab biosimilar, recombinant humanized anti-TNF-alpha monoclonal antibody, certolizumab pegol, golimumab, ozoralizumab, AT-132, etanercept biosimilar, ISIS-104838, ISU-202, CT-P17, MB-612, Debio-0512, anti-TNF alpha human monoclonal antibody, infliximab biobetter, UB-721, KN-002, DA-3113, BX-2922, R-TPR-015, BOW-050, PF-06410293, CKD-760, CHS-1420, GS-071, ABP-710, STI-002, BOW-015, FKB-327, BAX-2200, HLX-03, BI-695501, CNTO-148, MYL-1401AABP-501, HOT-3010, BAX-2923, SCH-215596, ABT-D2E7, BAT-1406, XPro-1595, Atsttrin, SSS-07, golimumab biosimilar, TA-101, adalimumab follow-on biologic, BLX-1002, ABX-0401, TAQ-588, golimumab biosimilar, TeHL-1, placulumab, PMI-001, tgAAV-TNFR:Fc, K-832, CYT-007-TNFQb, SSR-150106, PassTNF, Verigen, DOM-0200, DOM-0215, AME-527, anti-TNF-alpha mAb, GENZ-38167, BLX-1028, CYT-020-TNFQb, CC-1080, CC-1069; TNF alpha ligand modulators, such as MM-A01-01, CDP-571, camobucol; TNF antagonists, such as etanercept, certolizumab pegol, etanercept follow-on biologic, etanercept biosimilar, DNX-114, TNF antagonist with IL-12 antagonist (rheumatoid arthritis), University of Oxford, BN-006, SCB-131, pegsunercept, GBL-5b, ACE-772, onercept, DE-096, PN-0615,

lenercept, ITF-1779, MDL-201112, BAX-2200, SCB-808, DA-3853, HD-203; TNF gene inhibitors, such as GIBH-R-001-2; TNF receptor modulators, such as recombinant TNF receptor 2-Fc fusion protein mutant, T-0001, tgAAV-TNFR:Fc; TNFSF11 gene inhibitors, such as denosumab; Transcription factor p65 inhibitors, such as REM-1086; Transcription factor RelB inhibitors, such as REM-1086; Transferrin modulators, such as methotrexate, MBP-Y003; Tumor necrosis factor 13C receptor antagonists, such as VAY-736; Tumor necrosis factor 15 ligand inhibitors, such as anti-TL1A antibodies (rheumatoid arthritis/inflammatory bowel disease), NIAMS; Tumor necrosis factor ligand 13 inhibitors, such as atacicept; Tumor necrosis factor ligand inhibitors, such as ABBV-257, etanercept biosimilar, ABT-122; Type I IL-1 receptor antagonists, such as anakinra, anakinra biosimilar, anakinra follow-on biologic, AXXO; Type I TNF receptor antagonists, such as NM-9405; Type II TNF receptor modulators, such as etanercept, SCB-131, etanercept biosimilar, etanercept follow-on biologic, BAX-2200, SCB-808, LBEC-0101, DMB-3853, DWP-422, BT-D001, DA-3853; Unspecified GPCR agonists, such as NCP-70X; VEGF receptor antagonists, such as 2-methoxyestradiol and NSC-650853, SL-1026; VEGF-2 receptor antagonists, such as CG-026806; VEGF-2 receptor modulators, such as VEGFR2 neutralizing antibody (rheumatoid arthritis), University of Rochester; VEGF-B ligand inhibitors, such as CSL-346; X-linked inhibitor of apoptosis protein inhibitors, such as IAP inhibitors (oral), Pharmascience; and Zap70 tyrosine kinase inhibitors, such as MK-8457, CT-5332.

## 20 **COMBINATIONS FOR METABOLIC DISEASES OR CONDITIONS**

Examples of metabolic disorders include, without limitation, diabetes, including type I and type II diabetes, metabolic syndrome, dyslipidemia, obesity, glucose intolerance, hypertension, elevated serum cholesterol, and elevated triglycerides. Examples of therapeutic agents used to treat metabolic disorders include antihypertensive agents and lipid lowering agents. Additional therapeutic agents used to treat metabolic disorders include insulin, 25 sulfonylureas peroxisome proliferator activated receptor gamma (PPAR- $\gamma$ ) agonists, such as thiazolidinediones such as pioglitazones, biguanides, alpha-glucosidase inhibitors, Vitamin E and incretin mimetics. Thus, one aspect of the disclosure is a method of treating a metabolic disease comprising administering a compound of the disclosure in combination with one or more 30 compounds useful for the treatment of metabolic diseases to a subject, particularly a human subject, in need thereof.

## PHARMACEUTICAL COMPOSITIONS

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations (compositions). The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington’s Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with inactive ingredients (e.g., a carrier, pharmaceutical excipient, etc.) which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

In certain embodiments, formulations suitable for oral administration are presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient.

In certain embodiments, the pharmaceutical formulations include one or more compounds of the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium,

povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay  
5 disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

The amount of active ingredient that is combined with the inactive ingredients to produce a dosage form will vary depending upon the host treated and the particular mode of  
10 administration. For example, in some embodiments, a dosage form for oral administration to humans contains approximately 1 to 1000 mg of active material formulated with an appropriate and convenient amount of carrier material (e.g., inactive ingredient or excipient material). In certain embodiments, the carrier material varies from about 5 to about 95% of the total compositions (weight: weight). In some embodiments, the pharmaceutical compositions  
15 described herein contain about 1 to 800 mg, 1 to 600 mg, 1 to 400 mg, 1 to 200 mg, 1 to 100 mg or 1 to 50 mg of the compound of Formula I, or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical compositions described herein contain not more than about 400 mg of the compound of Formula I. In some embodiments, the pharmaceutical compositions described herein contain about 100 mg of the compound of Formula I, or a  
20 pharmaceutically acceptable salt thereof.

It should be understood that in addition to the ingredients particularly mentioned above the formulations disclosed herein may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

25 Veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier are further provided.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may  
30 be administered orally, parenterally or by any other desired route.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses), the method

of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies.

## ROUTES OF ADMINISTRATION

One or more compounds of Formula I (herein referred to as the active ingredients), or a pharmaceutically acceptable salt thereof, are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally. Accordingly, in one embodiment, the pharmaceutical compositions described herein are oral dosage forms. In certain embodiments, the pharmaceutical compositions described herein are oral solid dosage forms.

### Formulation Example 1

Hard gelatin capsules containing the following ingredients are prepared:

Ingredient	Quantity (mg/capsule)
Active Ingredient	30.0
Starch	305.0
Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules.

### Formulation Example 2

A tablet Formula is prepared using the ingredients below:

Ingredient	Quantity (mg/tablet)
Active Ingredient	25.0
Cellulose, microcrystalline	200.0
Colloidal silicon dioxide	10.0
Stearic acid	5.0

The components are blended and compressed to form tablets.

**Formulation Example 3**

A dry powder inhaler formulation is prepared containing the following components:

	Ingredient	Weight %
	Active Ingredient	5
5	Lactose	95

The active ingredient is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

**Formulation Example 4**

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

	Ingredient	Quantity (mg/tablet)
	Active Ingredient	30.0 mg
	Starch	45.0 mg
	Microcrystalline cellulose	35.0 mg
10	Polyvinylpyrrolidone	
	(as 10% solution in sterile water)	4.0 mg
	Sodium carboxymethyl starch	4.5 mg
	Magnesium stearate	0.5 mg
	Talc	1.0 mg
15	Total	120 mg

The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50 °C to 60 °C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

**Formulation Example 5**

Suppositories, each containing 25 mg of active ingredient are made as follows:

	Ingredient	Amount
5	Active Ingredient	25 mg
	Saturated fatty acid glycerides to	2,000 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

10

**Formulation Example 6**

Suspensions, each containing 50 mg of active ingredient per 5.0 mL dose are made as follows:

	Ingredient	Amount
	Active Ingredient	50.0 mg
15	Xanthan gum	4.0 mg
	Sodium carboxymethyl cellulose (11%)	
	Microcrystalline cellulose (89%)	50.0 mg
	Sucrose	1.75 g
	Sodium benzoate	10.0 mg
20	Flavor and Color	q.v.
	Purified water to	5.0 mL

The active ingredient, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

25

**Formulation Example 7**

A subcutaneous formulation may be prepared as follows:

	Ingredient	Quantity
	Active Ingredient	5.0 mg
5	Corn Oil	1.0 mL

**Formulation Example 8**

An injectable preparation is prepared having the following composition:

	Ingredients	Amount
	Active ingredient	2.0 mg/mL
10	Mannitol, USP	50 mg/mL
	Gluconic acid, USP	q.s. (pH 5-6)
	water (distilled, sterile)	q.s. to 1.0 mL
	Nitrogen Gas, NF	q.s.

**Formulation Example 9**

15 A topical preparation is prepared having the following composition:

	Ingredients	grams
	Active ingredient	0.2-10
	Span 60	2.0
	Tween 60	2.0
20	Mineral oil	5.0
	Petrolatum	0.10
	Methyl paraben	0.15
	Propyl paraben	0.05
	BHA (butylated hydroxy anisole)	0.01
25	Water	q.s. to 100

All of the above ingredients, except water, are combined and heated to 60°C with stirring. A sufficient quantity of water at 60°C is then added with vigorous stirring to emulsify the ingredients and water then added q.s. 100 g.

### Formulation Example 10

#### 5 Sustained Release Composition

	Ingredient	Weight Range%
	Active ingredient	50-95
	Microcrystalline cellulose (filler)	1-35
	Methacrylic acid copolymer	1-35
10	Sodium hydroxide	0.1-1.0
	Hydroxypropyl methylcellulose	0.5-5.0
	Magnesium stearate	0.5-5.0

Sustained release formulations of this disclosure may be prepared as follows: compound and pH-dependent binder and any optional excipients are intimately mixed (dry-blended). The dry-blended mixture is then granulated in the presence of an aqueous solution of a strong base which is sprayed into the blended powder. The granulate is dried, screened, mixed with optional lubricants (such as talc or magnesium stearate) and compressed into tablets. Preferred aqueous solutions of strong bases are solutions of alkali metal hydroxides, such as sodium or potassium hydroxide, preferably sodium hydroxide, in water (optionally containing up to 25% of water-miscible solvents such as lower alcohols).

The resulting tablets may be coated with an optional film-forming agent, for identification, taste-masking purposes and to improve ease of swallowing. The film forming agent will typically be present in an amount ranging from between 2% and 4% of the tablet weight. Suitable film-forming agents are well known to the art and include hydroxypropyl methylcellulose, cationic methacrylate copolymers (dimethylaminoethyl methacrylate/methyl-butyl methacrylate copolymers - Eudragit® E - Röhm. Pharma) and the like. These film-forming agents may optionally contain colorants, plasticizers and other supplemental ingredients.

The compressed tablets preferably have a hardness sufficient to withstand 8 Kp compression. The tablet size will depend primarily upon the amount of compound in the tablet. The tablets will include from 300 to 1100 mg of compound free base. Preferably, the tablets will

include amounts of compound free base ranging from 400-600 mg, 650-850 mg and 900-1100 mg.

In order to influence the dissolution rate, the time during which the compound containing powder is wet mixed is controlled. Preferably the total powder mix time, i.e., the time during which the powder is exposed to sodium hydroxide solution, will range from 1 to 10 minutes and preferably from 2 to 5 minutes. Following granulation, the particles are removed from the granulator and placed in a fluid bed dryer for drying at about 60°C.

### Formulation Example 11

A tablet Formula Is prepared using the ingredients below:

Ingredient	Quantity (mg/tablet)
Active Ingredient	300.0
Cellulose, microcrystalline	100.0
Colloidal silicon dioxide	10.0
Stearic acid	5.0

The components are blended and compressed to form tablets.

### EXAMPLES

The following examples are included to demonstrate specific embodiments of the disclosure. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques to function well in the practice of the disclosure, and thus can be considered to constitute specific modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

#### *List of Abbreviations and Acronyms*

Abbreviation	Meaning
°C	Degree Celsius
Ac	Acetyl
aq.	Aqueous

ATP	Adenosine triphosphate
B <sub>2</sub> Pin <sub>2</sub>	Bis(pinacolato)diboron
BOC	tert-Butoxycarbonyl
Br	Broad
BSA	Bovine serum albumin
d	Doublet
DCM	Dichloromethane
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
DIPEA	N,N-Diisopropylethylamine (Hünig's Base)
DMA	Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dt	Doublet-triplet
DTT	Dithiothreitol (Cleland's reagent)
EC <sub>50</sub>	The half maximal effective concentration
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EDTA	Ethylenediaminetetraacetic acid
EGFR	Epidermal growth factor receptor
Eq	Equivalents
ES/MS	Electrospray mass spectrometry
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol (Ethyl alcohol)
FBS	Fetal bovine serum

g	Grams
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HEPES	2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid
HCl	Hydrochloric acid
HPLC	High pressure liquid chromatography
Hrs	Hours
HTRF®	Homogeneous time resolved fluorescence, a registered trademark of Cisbio Bioassays, parmarcel boiteux 30200 codolet, France
Hz	Hertz
IBD	Inflammatory bowel disease
IC <sub>50</sub>	Half-maximal inhibitory concentration
i-pr	Isopropyl
J	Coupling constant (MHz)
K <sub>3</sub> PO <sub>4</sub>	Tripotasium phosphate
KOtBu	Potassium tert-butoxide
KOAc	Potassium Acetate
LCMS	Liquid chromatography–mass spectrometry
Lawesson's Reagent	2,4-Bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide
Li HMDS	Lithium bis(trimethylsilyl)amide
LiOH	Lithium hydroxide
LiI	Lithium iodide
LPS	Lipopolysaccharide
M	Molar

m	multiplet
M+	Mass peak
M+H+	Mass peak plus hydrogen
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol (Methyl alcohol)
MeLi	Methyl lithium
MeMgX	Methylmagnesium halide (Grignard reagent), where X is Fluoro, Chloro, Bromo or Iodo
Me <sub>6</sub> Sn <sub>2</sub>	Hexamethyldistannane (hexamethylditin)
mg	Milligram
MgSO <sub>4</sub>	Magnesium sulfate
MHz	Megahertz
Min	Minute
ml/mL	Milliliter
mM	Millimolar
mmol	Millimole
MS	Mass spectroscopy
MsCl	Mesyl chloride
NBS	N-Bromosuccinimide
n-	Normal
nBu/Bu	n-Butyl (normal Butyl)
n-BuLi	n-Butyl Lithium
NaH	Sodium hydride
NaHCO <sub>3</sub>	Sodium bicarbonate
NaN <sub>3</sub>	Sodium azide
Na <sub>3</sub> PO <sub>4</sub>	Trisodium phosphate

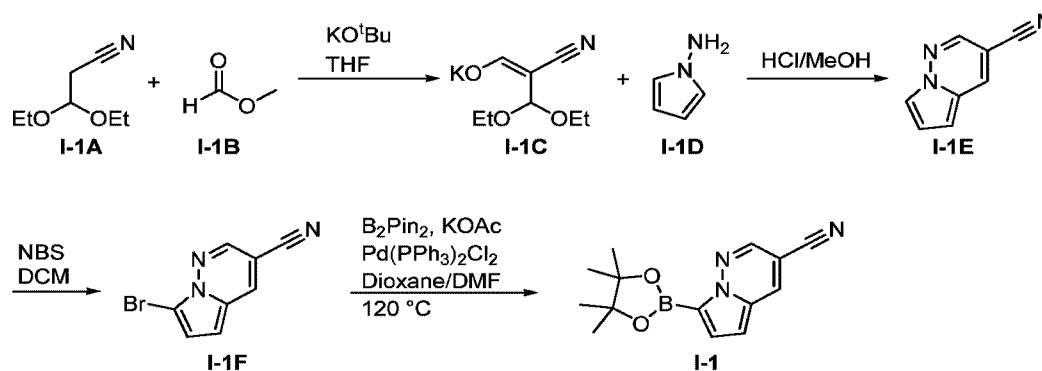
	Na <sub>2</sub> SO <sub>4</sub>	Sodium sulfate
	nL	Nanoliter
	nm	Nanometer
	NMP	1-methylpyrrolidin-2-one
	NMR	Nuclear magnetic resonance
	NP-40	Nonyl phenoxy polyethoxy ethanol
IPent	Pd-PEPPSI™ –	[1,3-bis(2,6-di-3-pentylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
	Pen-Strep	Penicillin-Streptomycin (5,000 units of penicillin G sodium salt, and 5,000 µg streptomycin sulfate in 0.85% saline)
	Ph	Phenyl
	q	Quartet
	q.s.	Quantity sufficient to achieve a stated function
	RP	Reverse phase
	RPMI	Roswell Park Memorial Institute medium
	Rt	Room temperature
	s	Singlet
	sat.	Saturated
	Selectfluor®	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis (a trademark of Air Products and Chemicals)
	SFC	Supercritical fluid chromatography
Thiol	SiliaMetS®	Silica-based Palladium scavenger, registered trademark of Silicycle
	T	Triplet

THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
XPhos Pd G3	(2-Dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate

## EXPERIMENTAL PROCEDURES

### Synthesis of Intermediates

#### Preparation of Intermediate I-1:



#### 5      **3,3-Diethoxy-2-formylpropionitrile Potassium Salt (I-1C):**

To a stirred solution of 3,3-diethoxypropane-nitrile (**I-1A**, 283.80 g, 1.98 moles) and methyl formate (**I-1B**, 148.80 g, 2.48 moles) in anhydrous THF (1.1 L) at 10 °C was added 1.0 M potassium tert-butoxide in THF (2.2 L, 2.2 moles). The temperature was maintained in the range of 10 °C to 15 °C throughout the 45 minute addition. Following the addition, the resulting slurry was stirred for 2 hours at ambient temperature. Hexane (400 mL) was then added and stirring was continued for another 20 min. The slurry was filtered and the cake washed with 1/1 hexanes/THF and dried overnight at 60 °C in a vacuum oven to provide **I-1C**. <sup>1</sup>H-NMR (CD<sub>3</sub>OD) was consistent with the desired structure.

#### 15      **Pyrrolo[1,2-b]pyridazine-3-carbonitrile (I-1E):**

A stirred suspension of 3,3-diethoxy-2-formylpropionitrile potassium salt (**I-1C**, 5.10 g, 24.36 mmol) was cooled to 0 °C, and concentrated HCl (7.11 mL, 85.26 mmol) was added

dropwise at such a rate that the internal temperature of the reaction did not go above 20 °C. After addition was complete, the reaction was stirred at room temperature for 20 minutes. To this reaction mixture was added a solution of 1-aminopyrrole (**I-1D**, 1.00 g, 12.18 mmol) in methanol (4.0 mL). After addition, the reaction mixture was refluxed at 90 °C for 2 hours. When heating was complete, the reaction was cooled to room temperature and concentrated to about half of the original volume. Saturated aqueous sodium bicarbonate was added carefully to the resulting residue until bubbling stopped. The solution was extracted with two portions of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, concentrated *in vacuo*, and the resulting residue was purified by silica gel chromatography (eluent: EtOAc/hexanes) to provide **I-1E**.

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.16 - 8.03 (m, 2H), 7.93 (ddd, J = 2.6, 1.4, 0.6 Hz, 1H), 7.04 (dd, J = 4.5, 2.7 Hz, 1H), 6.84 (dd, J = 4.6, 1.4 Hz, 1H).

**7-bromopyrrolo[1,2-b]pyridazine-3-carbonitrile (I-1F):**

To a solution of pyrrolo[1,2-b]pyridazine-3-carbonitrile (**I-1E**, 840.0 mg, 5.9 mmol) in MeCN (30 mL) at room temperature was added N-bromosuccinimide in one portion. The reaction was stirred at room temperature for 30 minutes then poured into saturated aqueous sodium bicarbonate. The solution was concentrated *in vacuo* to remove the acetonitrile. The resulting aqueous layer was extracted with three portions of EtOAc. The combined organic layers were dried over sodium sulfate, filtered, concentrated *in vacuo*, and purified by silica gel chromatography (eluent: EtOAc/hexanes) to provide **I-1F**.

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.28 (d, J = 2.1 Hz, 1H), 8.10 (d, J = 2.1 Hz, 1H), 7.12 (d, J = 4.8 Hz, 1H), 6.93 (d, J = 4.8 Hz, 1H).

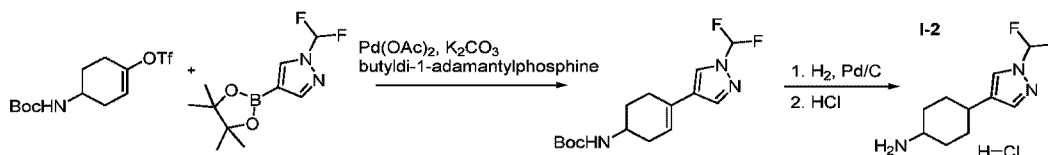
**7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[1,2-b]pyridazine-3-carbonitrile (I-1):**

A microwave vial was charged with 7-bromopyrrolo[1,2-b]pyridazine-3-carbonitrile (**I-1F**, 416.5 mg, 1.9 mmol), bis(pinacolato)diboron (762.1 mg, 3.0 mmol), potassium acetate (552.3 mg, 5.6 mmol), and bis(triphenylphosphine)palladium(II) dichloride (65.8 mg, 0.094 mmol). Dioxane (8.0 mL) and DMF (4.0 mL) were added, and the reaction mixture was degassed with bubbling argon for 2 minutes. The vial was sealed and the reaction was heated at 120 °C in a microwave reactor for 60 minutes. After cooling, the reaction mixture was filtered and concentrated *in vacuo*. The resulting residue was partitioned between EtOAc and water. The aqueous layer was extracted with a second portion of EtOAc, and the combined organic layers were dried over sodium sulfate, filtered through a plug of Celite, and concentrated *in vacuo*. The

resulting residue was purified by silica gel chromatography (eluent: EtOAc/hexanes) to provide **I-1**.

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  8.31 (d, *J* = 2.3 Hz, 1H), 8.14 (d, *J* = 2.2 Hz, 1H), 7.52 (d, *J* = 4.6 Hz, 1H), 6.84 (d, *J* = 4.6 Hz, 1H), 1.41 (s, 12H).

#### 5 Preparation of Intermediate I-2:



#### **tert-butyl (4-(1-(difluoromethyl)-1H-pyrazol-4-yl)cyclohex-3-en-1-yl)carbamate:**

4-((tert-butoxycarbonyl)amino)cyclohex-1-en-1-yl trifluoromethanesulfonate (3.52 g, 10.2 mmol), 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (3.11 g, 12.7 mmol), Pd(OAc)<sub>2</sub> (0.11 g, 0.51 mmol), butyldi-1-adamantylphosphine (0.37 g, 1.02 mmol), and K<sub>2</sub>CO<sub>3</sub> (2.82 g, 10.4 mmol) were combined in a sealed tube along with DME (20 mL) and water (10 mL) and the resulting slurry was degassed with argon then heated at 80 °C for 16h. The reaction contents were diluted with EtOAc (70 mL), washed with brine (1 x 15 mL), and dried over MgSO<sub>4</sub>. The crude residue was then purified via silica gel chromatography (eluent: EtOAc/hexanes) to give the product tert-butyl (4-(1-(difluoromethyl)-1H-pyrazol-4-yl)cyclohex-3-en-1-yl)carbamate.

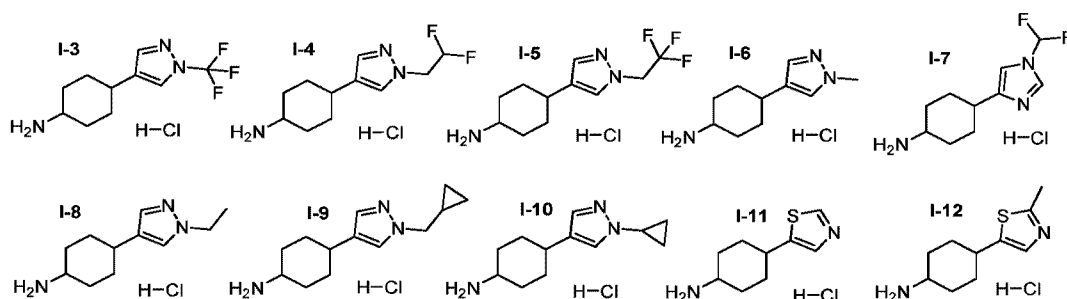
ES/MS: 258.0 (M+H<sup>+</sup>).

#### **4-(1-(difluoromethyl)-1H-pyrazol-4-yl)cyclohexan-1-amine hydrochloride (I-2):**

A suspension of tert-butyl (4-(1-(difluoromethyl)-1H-pyrazol-4-yl)cyclohex-3-en-1-yl)carbamate (0.23 g, 0.75 mmol) in EtOH (15 mL) was degassed with argon and vacuum. Pd/C (10%, 91 mg, 0.086 mmol) was added and the mixture was stirred with a balloon of H<sub>2</sub> overnight. The reaction was filtered over a Celite plug, rinsed with EtOAc and the filtrate was concentrated to give tert-butyl (4-(1-(difluoromethyl)-1H-pyrazol-4-yl)cyclohexyl)carbamate which was carried forward without further purification assuming quantitative yield. To a solution of tert-butyl (4-(1-(difluoromethyl)-1H-pyrazol-4-yl)cyclohexyl)carbamate (0.24 g, 0.75 mmol) in DCM (6 mL) was added HCl (4.0M in dioxane, 3 mL, 12 mmol) and the resulting solution stirred at room temperature for 16h. Upon completion the reaction mixture was concentrated to dryness to give 4-(1-(difluoromethyl)-1H-pyrazol-4-yl)cyclohexan-1-amine hydrochloride (**I-2**) which was used without further purification.

ES/MS: 216.1 (M+H<sup>+</sup>).

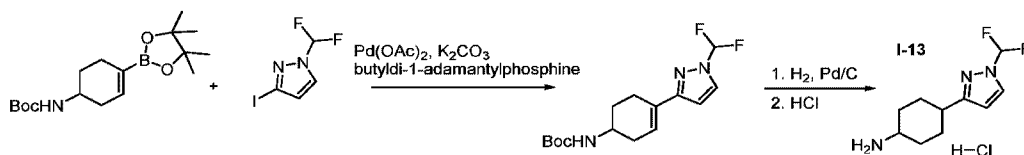
**Preparation of Intermediate I-3 to I-12:**



Intermediates **I-3** through **I-12** were prepared in the manner described for **I-2**

- 5 substituting 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole with the appropriately substituted heteroaryl boronic ester.

**Preparation of Intermediate I-13:**



**tert-butyl (4-(1-(difluoromethyl)-1H-pyrazol-3-yl)cyclohex-3-en-1-yl)carbamate:**

- 10 tert-butyl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)carbamate (0.60 g, 1.86 mmol), 1-(difluoromethyl)-3-iodo-1H-pyrazole (0.50 g, 2.05 mmol), Pd(OAc)<sub>2</sub> (22 mg, 0.098 mmol), butyldi-1-adamantylphosphine (78 mg, 0.22 mmol), and K<sub>2</sub>CO<sub>3</sub> (0.51 g, 3.71 mmol) were combined in a sealed tube along with DME (10 mL) and water (5 mL) and the resulting slurry was degassed with argon then heated at 80 °C for 18h. The reaction contents  
15 were diluted with EtOAc (40 mL), washed with brine (1 x 10 mL), and dried over MgSO<sub>4</sub>. The crude residue was then purified via silica gel chromatography (eluent: EtOAc/hexanes) to give the product tert-butyl (4-(1-(difluoromethyl)-1H-pyrazol-3-yl)cyclohex-3-en-1-yl)carbamate.

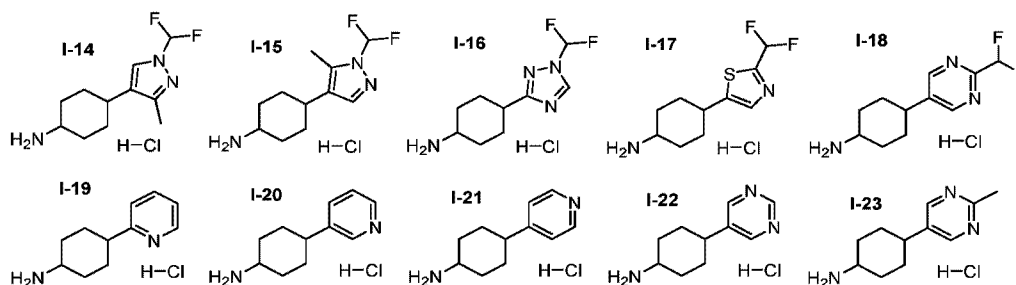
ES/MS: 313.7 (M+H<sup>+</sup>).

**4-(1-(difluoromethyl)-1H-pyrazol-3-yl)cyclohexan-1-amine hydrochloride (I-13):**

- 20 A suspension of tert-butyl (4-(1-(difluoromethyl)-1H-pyrazol-3-yl)cyclohex-3-en-1-yl)carbamate (0.50 g, 0.160 mmol) in EtOH (15 mL) was degassed with argon and vacuum. Pd/C (10%, 85 mg, 0.080 mmol) was added and the mixture was stirred with a balloon of H<sub>2</sub> overnight. The reaction was filtered over a Celite plug, rinsed with EtOAc and the filtrate was concentrated to give tert-butyl (4-(1-(difluoromethyl)-1H-pyrazol-3-yl)cyclohexyl)carbamate

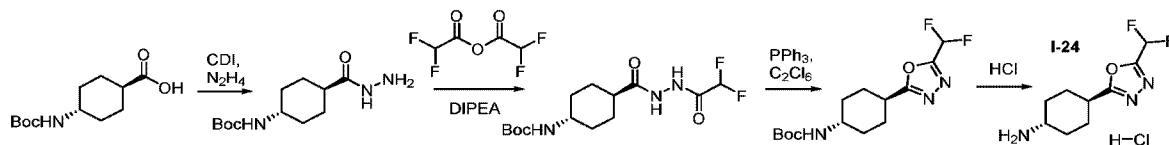
which was carried forward without further purification assuming quantitative yield. To a solution of tert-butyl (4-(1-(difluoromethyl)-1H-pyrazol-3-yl)cyclohexyl)carbamate (0.50 g, 1.58 mmol) in DCM (10 mL) was added HCl (4.0M in dioxane, 2.9 mL, 11.6 mmol) and the resulting solution stirred at room temperature for 16h. Upon completion the reaction mixture was concentrated to dryness to give 4-(1-(difluoromethyl)-1H-pyrazol-3-yl)cyclohexan-1-amine hydrochloride (**I-13**) which was used without further purification.

**Preparation of Intermediates I-14 to I-23:**



Intermediates **I-14** through **I-23** were prepared in the manner described for **I-13** substituting 1-(difluoromethyl)-3-iodo-1H-pyrazole with the appropriately substituted heteroaryl bromide or iodide.

**Preparation of Intermediate I-24:**



**tert-butyl ((1r,4r)-4-(hydrazinecarbonyl)cyclohexyl)carbamate:**

To a solution of (1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxylic acid (10.0 g, 41.1 mmol) in THF (360 mL) was added 1,1'-carbonyldiimidazole (10.7 g, 65.8 mmol) as a single portion and the resulting mixture stirred for 16h at room temperature. Hydrazine hydrate (10.0 mL, 206 mmol) was then added as a single portion. After 15 minutes approximately 200 mL THF was removed by rotary evaporation and the resulting slurry filtered rinsing with THF. The solid was dried under vacuum to give tert-butyl ((1r,4r)-4-(hydrazinecarbonyl)cyclohexyl)carbamate which was used without further purification.

ES/MS: 202.2 (M+H<sup>+</sup>).

**tert-butyl ((1r,4r)-4-(2-(2,2-difluoroacetyl)hydrazine-1-carbonyl)cyclohexyl)carbamate:**

To a solution of tert-butyl ((1r,4r)-4-(hydrazinecarbonyl)cyclohexyl)carbamate (1.50 g, 5.83 mmol) and diisopropylethylamine (2.6 mL, 14.9 mmol) in THF (20 mL) was added  
5 difluoroacetic anhydride (0.93 mL, 7.43 mmol) and the reaction mixture allowed to stir at room temperature. After 30 minutes additional difluoroacetic anhydride (0.40 mL, 3.20 mmol) was added and the reaction mixture allowed to stir for 30 minutes. The reaction mixture was then poured into water (20 mL), extracted with EtOAc (2 x 40 mL), washed with brine (1 x 15 mL), dried over MgSO<sub>4</sub>, filtered and concentrated to give crude tert-butyl ((1r,4r)-4-(2-(2,2-  
10 difluoroacetyl)hydrazine-1-carbonyl)cyclohexyl)carbamate which was used without further purification.

ES/MS: 280.0 (M+H<sup>+</sup>).

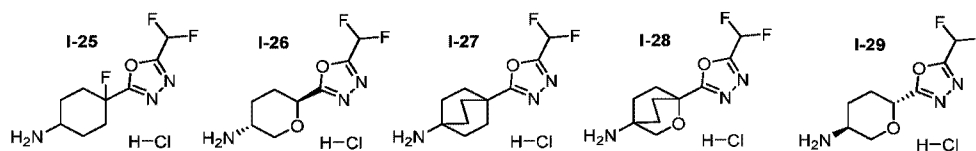
**tert-butyl ((1r,4r)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexyl)carbamate:**

To a solution of tert-butyl ((1r,4r)-4-(2-(2,2-difluoroacetyl)hydrazine-1-  
15 carbonyl)cyclohexyl)carbamate (1.66 g, 4.96 mmol) in dry acetonitrile (40 mL) was added sequentially triphenylphosphine (3.90 g, 14.9 mmol), hexachloroethane (1.76 g, 7.34 mmol) and diisopropylethylamine (5.2 mL, 29.7 mmol) and the resulting solution allowed to stir for 15 minutes at room temperature. Upon completion the reaction mixture was poured into saturated aqueous NH<sub>4</sub>Cl (30 mL, and extracted with EtOAc (2 x 60 mL). The combined organics were  
20 washed with brine (1 x 15 mL), dried over MgSO<sub>4</sub>, filtered and concentrated to give a crude residue which was further purified using silica gel chromatography (eluent: EtOAc/hexanes) to give the product tert-butyl ((1r,4r)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-  
yl)cyclohexyl)carbamate.

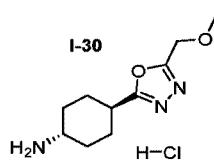
**(1r,4r)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexan-1-amine hydrochloride (I-24):**

Tert-butyl ((1r,4r)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexyl)carbamate (1.26 g, 3.96 mmol) was dissolved in HCl solution (4.0M in dioxane, 12 mL, 48 mmol) and the resulting mixture was stirred in a preheated 50 °C heating block for 30 minutes. Upon  
completion the suspension was filtered directly washing with dioxane (1 x 4 mL) and the solid  
30 dried under vacuum to give (1r,4r)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexan-1-amine hydrochloride (I-24) which was used without further purification.

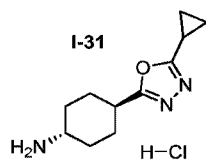
ES/MS: 218.0 (M+H<sup>+</sup>).

**Preparation of Intermediates I-25 to I-29:**

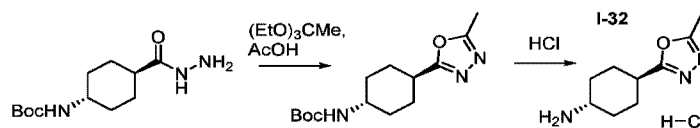
Intermediates **I-25** through **I-29** were prepared in the manner described for **I-24** substituting (1*r*,4*r*)-4-((*tert*-butoxycarbonyl)amino)cyclohexane-1-carboxylic acid with the  
5 appropriately substituted carboxylic acid.

**Preparation of Intermediate I-30:**

Intermediate **I-30** was prepared in the manner described for **I-24**, substituting difluoroacetic anhydride with 2-methoxyacetyl chloride in the second step.

**10 Preparation of Intermediate I-31:**

Intermediate **I-31** was prepared in the manner described for **I-24**, substituting difluoroacetic anhydride with cyclopropane carbonyl chloride in the second step.

**Preparation of Intermediate I-32:**

15

**(1*r*,4*r*)-4-(5-methyl-1,3,4-oxadiazol-2-yl)cyclohexan-1-amine hydrochloride:**

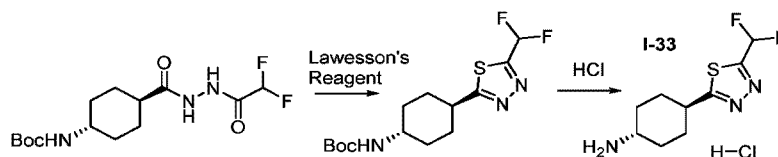
To a solution of *tert*-butyl ((1*r*,4*r*)-4-(hydrazinecarbonyl)cyclohexyl)carbamate (0.15 g, 0.58 mmol) in triethylorthoacetate (2 mL) was added catalytic acetic acid (0.05 mL) and the resulting solution heated to 125 °C for 4h. The reaction mixture was concentrated directly and  
20 the resulting crude *tert*-butyl ((1*r*,4*r*)-4-(5-methyl-1,3,4-oxadiazol-2-yl)cyclohexyl)carbamate was dissolved in HCl solution (4.0M in dioxane, 3 mL, 12 mmol) and stirred for 12h at room temperature. The reaction mixture was concentrated directly and the resulting (1*r*,4*r*)-4-(5-

methyl-1,3,4-oxadiazol-2-yl)cyclohexan-1-amine hydrochloride was used without further purification.

ES/MS: 182.0 (M+H<sup>+</sup>).

**Preparation of Intermediate I-33:**

5



**tert-butyl ((1r,4r)-4-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)cyclohexyl)carbamate:**

To a solution of tert-butyl ((1r,4r)-4-(2-(2,2-difluoroacetyl)hydrazine-1-carbonyl)cyclohexyl)carbamate (0.21 g, 0.63 mmol) in THF (10 mL) was added Lawesson's reagent (0.30 g, 0.75 mmol) and the resulting solution heated at 50 °C for 16h. Upon completion the reaction mixture was poured into water (10 mL, extracted with EtOAc (2 x 30 mL), washed with brine (10 mL), dried over MgSO<sub>4</sub> and concentrated. The crude residue was purified using silica gel chromatography (eluent: EtOAc/hexanes) to give the product tert-butyl ((1r,4r)-4-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)cyclohexyl)carbamate.

10

ES/MS: 333.9 (M+H<sup>+</sup>).

15

**(1r,4r)-4-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)cyclohexan-1-amine hydrochloride (I-33):**

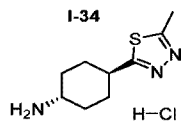
20

tert-butyl ((1r,4r)-4-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)cyclohexyl)carbamate (0.31 g, 0.39 mmol) was dissolved in HCl solution (4.0M in dioxane, 12 mL, 48 mmol) and the resulting mixture was stirred at room temperature for 1h. Upon completion the reaction contents were concentrated and dried under vacuum to give (1r,4r)-4-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)cyclohexan-1-amine hydrochloride (**I-33**) which was used without further purification.

ES/MS: 234.0 (M+H<sup>+</sup>).

**Preparation of Intermediate I-34:**

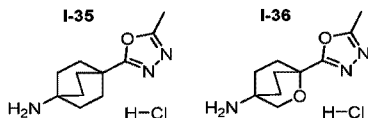
25



Intermediate **I-34** was prepared in the manner described for intermediate **I-33** substituting tert-butyl ((1r,4r)-4-(2-(2,2-difluoroacetyl)hydrazine-1-

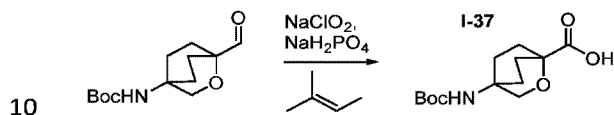
carbonyl)cyclohexyl)carbamate with tert-butyl ((1*r*,4*r*)-4-(2-acetylhydrazine-1-carbonyl)cyclohexyl)carbamate in the first step.

#### Preparation of Intermediates I-35 and I-36:



- 5 Intermediates **I-35** and **I-36** were prepared in the manner described for intermediate **I-32** substituting (1*r*,4*r*)-4-((tert-butoxycarbonyl)amino)cyclohexane-1-carboxylic acid with 4-((tert-butoxycarbonyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid and 4-((tert-butoxycarbonyl)amino)-2-oxabicyclo[2.2.2]octane-1-carboxylic acid respectively.

#### Preparation of Intermediate I-37:

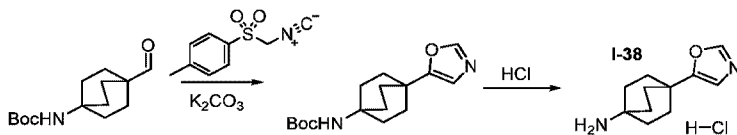


#### 4-((tert-butoxycarbonyl)amino)-2-oxabicyclo[2.2.2]octane-1-carboxylic acid (I-37):

- 15 To a solution of tert-butyl (1-formyl-2-oxabicyclo[2.2.2]octan-4-yl)carbamate (1.00 g, 3.92 mmol) in THF (10 mL) and tBuOH (10 mL) was added 2-methyl-2-butene (8.3 mL, 78.3 mmol) followed by NaH<sub>2</sub>PO<sub>4</sub> (3.76 g, 31.3 mmol) as a solution in water (5 mL) and finally sodium chlorite (1.06 g, 11.8 mmol) as a solution in water (5 mL). After 16h stirring at room temperature the reaction mixture was poured into saturated aqueous NH<sub>4</sub>Cl (15 mL), and extracted with EtOAc (2 x 40 mL). The combined organics were washed with brine (10 mL), dried over MgSO<sub>4</sub>, and concentrated to give 4-((tert-butoxycarbonyl)amino)-2-oxabicyclo[2.2.2]octane-1-carboxylic acid (**I-37**) which was used without further purification.

- 20 ES/MS: 216.0 (M+H<sup>+</sup>).

#### Preparation of Intermediate I-38:

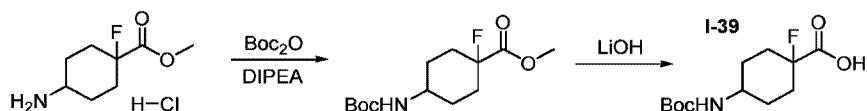


#### (1*r*,4*r*)-4-(oxazol-5-yl)cyclohexan-1-amine hydrochloride (I-38):

- 25 To a solution of tert-butyl (4-formylbicyclo[2.2.2]octan-1-yl)carbamate (0.80 g, 3.16 mmol) in MeOH (14 mL) was added p-toluenesulfonylmethylisocyanide (0.74 g, 3.79 mmol) and the resulting mixture heated at 85 °C for 12 hours. The mixture was poured into water (20

mL) and extracted with EtOAc (2 x 40mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. The resulting crude residue was purified by silica gel chromatography (eluent: EtOAc/hexanes) to give tert-butyl (4-(oxazol-5-yl)bicyclo[2.2.2]octan-1-yl)carbamate. This was then dissolved in HCl (4.0M in dioxane, 3 mL, 12 mmol) and stirred at room temperature for 3 hours after which the reaction mixture was concentrated to dryness directly to give (1r,4r)-4-(oxazol-5-yl)cyclohexan-1-amine hydrochloride (**I-38**) which was used without further purification.

#### Preparation of Intermediate I-39:



#### 10 methyl (1s,4s)-4-((tert-butoxycarbonyl)amino)-1-fluorocyclohexane-1-carboxylate:

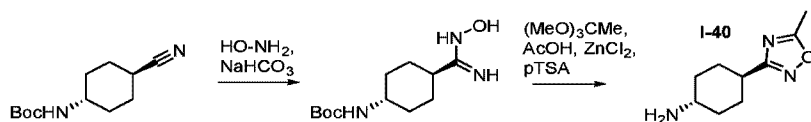
To a solution/suspension of methyl (1s,4s)-4-amino-1-fluorocyclohexane-1-carboxylate (1.00 g, 4.73 mmol) in DCM (10 mL) at 0 °C was added diisopropylethylamine (1.8 mL, 10.4 mmol) followed by Di-tert-butyl dicarbonate (1.13 g, 5.20 mmol). After 2h stirring at 0 °C The reaction mixture was poured into saturated aqueous NH<sub>4</sub>Cl (15 mL) and extracted with EtOAc (2 x 40 mL). The combined organics were washed with brine (1 x 15 mL), dried over MgSO<sub>4</sub> and concentrated to give methyl (1s,4s)-4-((tert-butoxycarbonyl)amino)-1-fluorocyclohexane-1-carboxylate which was used without further purification.

ES/MS: 219.9 (M+H<sup>+</sup>).

#### 20 (1s,4s)-4-((tert-butoxycarbonyl)amino)-1-fluorocyclohexane-1-carboxylic acid (**I-39**):

To a solution of methyl (1s,4s)-4-((tert-butoxycarbonyl)amino)-1-fluorocyclohexane-1-carboxylate (1.30 g, 4.72 mmol) in EtOH (10 mL) was added lithium hydroxide (0.34 g, 14.2 mmol) as a solution in water (4 mL) and the resulting solution stirred at room temperature for 3h. Upon completion the EtOH was removed by rotary evaporation and the resulting aqueous solution was acidified to pH ~2-3 using aqueous 1.0M HCl. The aqueous was then extracted with EtOAc (3 x 30 mL) and the combined organics washed with brine (1 x 15 mL), dried over MgSO<sub>4</sub> and concentrated to give (1s,4s)-4-((tert-butoxycarbonyl)amino)-1-fluorocyclohexane-1-carboxylic acid (**I-39**) which was used without further purification.

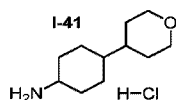
ES/MS: 206.0 (M+H<sup>+</sup>).

**Preparation of Intermediate I-40:****tert-butyl ((1r,4r)-4-(N-hydroxycarbamimidoyl)cyclohexyl)carbamate:**

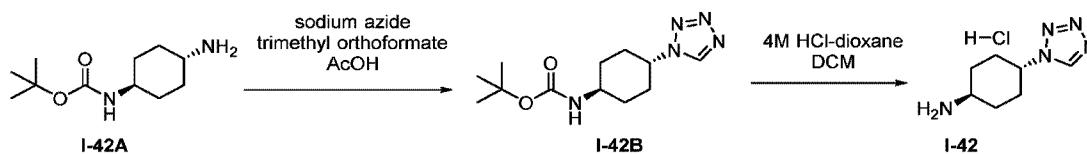
DMSO (40 mL) was added to hydroxylamine hydrochloride (1.55 g, 22.3 mmol) and the  
 5 resulting mixture was heated to 40 °C for 30 minutes. NaHCO<sub>3</sub> (1.87 g, 22.3 mmol) was added  
 as a single portion and the mixture then heated at 50 °C for 1h at which point a solution of tert-  
 butyl ((1r,4r)-4-cyanocyclohexyl)carbamate (0.50 g, 2.23 mmol) in DMSO (40 mL) was added  
 and the reaction mixture heated at 90 °C for 16h. After cooling, the reaction mixture was poured  
 10 into water (150 mL) and extracted with EtOAc (2 x 225 mL). The combined organic layers were  
 washed with water (2 x 10 mL, brine (1 x 50 mL), dried over MgSO<sub>4</sub> and concentrated to give  
 tert-butyl ((1r,4r)-4-(N-hydroxycarbamimidoyl)cyclohexyl)carbamate which was used without  
 further purification.

**(1r,4r)-4-(5-methyl-1,2,4-oxadiazol-3-yl)cyclohexan-1-amine (I-40):**

To a solution of tert-butyl ((1r,4r)-4-(N-hydroxycarbamimidoyl)cyclohexyl)carbamate  
 15 (0.20 g, 0.78 mmol) in acetonitrile (5 mL) was added sequentially p-toluenesulfonic acid (44  
 mg, 0.23 mmol) and ZnCl<sub>2</sub> (32 mg, 0.23 mmol). The resulting reaction mixture was heated at 70  
 °C for 6h, poured into saturated aqueous NaHCO<sub>3</sub> (5 mL, and extracted with EtOAc (2 x 25  
 mL). The combined organic layers were washed with brine (5 mL), dried over MgSO<sub>4</sub> and  
 concentrated to give (1r,4r)-4-(5-methyl-1,2,4-oxadiazol-3-yl)cyclohexan-1-amine (**I-40**) which  
 20 was used without further purification.

**Preparation of Intermediate I-41:**

Intermediate **I-41** was prepared in the manner described for **I-2** substituting 1-  
 (difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole with 2-(3,6-  
 25 dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

**Preparation of Intermediate I-42:****tert-butyl ((1r,4r)-4-(2H-4H-tetrazol-4-yl)cyclohexyl)carbamate (I-42B):**

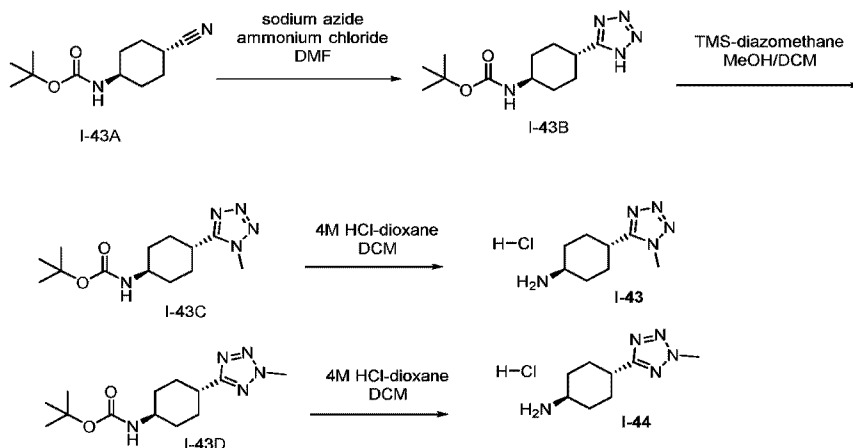
To a solution of tert-butyl ((1r,4r)-4-aminocyclohexyl)carbamate (**I-42A**, 1000 mg, 4.67 mmol), sodium azide (306 mg, 4.407 mmol), and trimethyl orthoformate (2350  $\mu$ l, 21.44 mmol), was added AcOH (3 mL). The reaction was heated at 70 deg for 48 hr. The reaction was diluted with water and carefully neutralized with saturated NaHCO<sub>3</sub> solution. The resulting precipitate was air-dried to give **I-42B**.

ES/MS: 267.9 (M<sup>+</sup>).

<sup>1</sup>H NMR (400 MHz, Chloroform-d)  $\delta$  8.60 (s, 1H), 4.51 (ddt, J = 12.1, 7.9, 3.9 Hz, 1H), 3.60 (s, 1H), 2.32 (dd, J = 32.5, 13.1 Hz, 4H), 1.97 (qd, J = 12.9, 3.5 Hz, 2H), 1.59 (s, 3H), 1.48 (s, 9H), 1.39 (td, J = 13.1, 12.5, 3.4 Hz, 2H).

**(1r,4r)-4-(1H-tetrazol-1-yl)cyclohexan-1-amine hydrochloride (I-42):**

To a solution of tert-butyl ((1r,4r)-4-(2H-4H-tetrazol-4-yl)cyclohexyl)carbamate (**I-42B**, 467.5 mg, 1.749 mmol) in DCM (10 mL) was added HCl (3.0 mL, 4.0M in dioxane). The reaction was stirred at rt overnight and concentrated to dryness to give **I-42**.

**Preparation of Intermediate I-43 and I-44:****tert-butyl ((1r,4r)-4-(1H-tetrazol-5-yl)cyclohexyl)carbamate (I-43B):**

To a solution of tert-butyl ((1r,4r)-4-cyanocyclohexyl)carbamate (**I-43A**, 1000 mg, 4.46

mmol) in DMF (15 mL), was added sodium azide (1014 mg, 15.6 mmol) and Ammonium chloride (835 mg, 15.6 mmol). The reaction was heated at 120 deg for 48 hr. The reaction was diluted with EtOAc and washed with LiCl 5% 3x. The organic extracts were dried over sodium sulfate, filtered, and concentrated to give **I-43B**

5 ES/MS: 268.0 (M+H<sup>+</sup>).

<sup>1</sup>H NMR (400 MHz, Chloroform-d)  $\delta$  4.42 (s, 1H), 3.48 (s, 1H), 2.42 (tt, J = 11.7, 3.5 Hz, 1H), 2.11 (dt, J = 12.2, 7.5, 3.7 Hz, 4H), 1.81 - 1.55 (m, 2H), 1.46 (s, 9H), 1.29 - 1.04 (m, 2H).

**tert-butyl ((1r,4r)-4-(1-methyl-1H-tetrazol-5-yl)cyclohexyl)carbamate (I-43C):**

10 **tert-butyl ((1R,4r)-4-((R)-2-methyl-5H-2 $\lambda^4$ -tetrazol-5-yl)cyclohexyl)carbamate (I-43D)**

To a solution of tert-butyl ((1r,4r)-4-(1H-tetrazol-5-yl)cyclohexyl)carbamate (**I-43B**, 638 mg, 2.387 mmol) in MeOH (15 mL) at 0 deg, was added 2M (Trimethylsilyl)diazomethane solution 2.0 M in hexanes (2500  $\mu$ l). The reaction was gradually warmed to room temp and stirred. The reaction was quenched carefully with AcOH until gas evolution stopped. The solution was diluted with EtOAc, washed with sat'd NaHCO<sub>3</sub>, dried with sodium sulfate, and purified by silica gel chromatography (eluent: EtOAc/hexanes) to provide minor product **I-43C** and major product **I-43D**

**I-43D** (major)

20 (M+H<sup>+</sup>) 281.9

<sup>1</sup>H NMR (400 MHz, Chloroform-d)  $\delta$  4.47 (s, 1H), 4.03 (s, 3H), 3.56 (s, 1H), 2.78 (tt, J = 12.1, 3.7 Hz, 1H), 2.34 - 2.15 (m, 3H), 2.15 - 1.98 (m, 3H), 1.89 (qd, J = 13.2, 3.4 Hz, 3H), 1.47 (s, 11H), 1.30 (qd, J = 12.7, 4.3 Hz, 3H).

**I-43C** (minor)

25 (M+H<sup>+</sup>) 281.9

<sup>1</sup>H NMR (400 MHz, Chloroform-d)  $\delta$  4.47 (d, J = 8.4 Hz, 1H), 4.31 (s, 3H), 3.52 (s, 1H), 2.89 (tt, J = 12.2, 3.4 Hz, 1H), 2.30 - 2.09 (m, 5H), 1.78 - 1.58 (m, 3H), 1.46 (s, 11H), 1.39 - 1.09 (m, 3H).

**(1r,4r)-4-(1-methyl-1H-tetrazol-5-yl)cyclohexan-1-amine hydrochloride (I-43)**

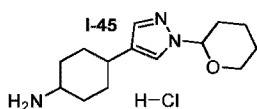
30 To a solution of tert-butyl ((1r,4r)-4-(1-methyl-1H-tetrazol-5-yl)cyclohexyl)carbamate (**I-43C**, 99.4 mg, 0.353 mmol) in DCM (5 mL) was added HCl (0.6 mL, 4.0M in dioxane). The

reaction was stirred at rt overnight and concentrated to dryness to give **I-43**.

**(1R,4r)-4-((R)-2-methyl-5H-2λ<sup>4</sup>-tetrazol-5-yl)cyclohexan-1-amine hydrochloride (I-44)**

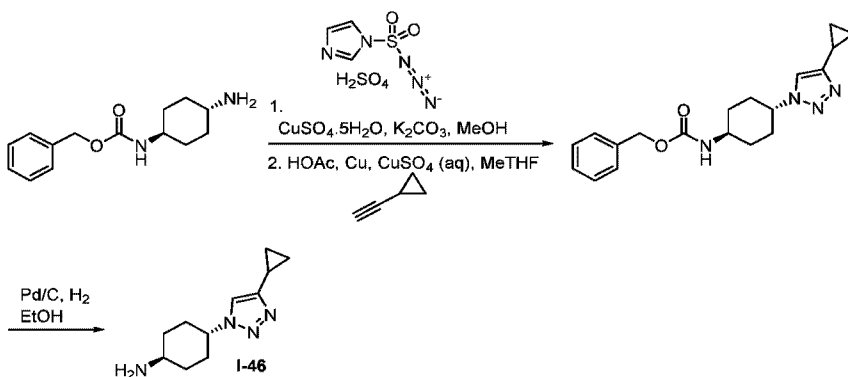
To a solution of tert-butyl ((1R,4r)-4-((R)-2-methyl-5H-2λ<sup>4</sup>-tetrazol-5-yl)cyclohexyl)carbamate (**I-43D**, 369.9 mg, 1.315 mmol) in DCM (8 mL) was added HCl (2.2 mL, 4.0M in dioxane). The reaction was stirred at rt overnight and concentrated to dryness to give **I-44**.

**Preparation of Intermediate I-45:**



Intermediate **I-45** was prepared in the manner described for **I-2** substituting 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole with 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole.

**Preparation of Intermediate I-46:**



**benzyl ((1r,4r)-4-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)cyclohexyl)carbamate:** To a solution of N-CBZ-trans-1,4-cyclohexanediamine (200 mg, 0.81 mmol), 1H-Imidazole-1-sulfonyl azide hydrogen sulfate (328 mg, 1.2 mmol), and potassium carbonate (334 mg, 2.4 mmol) in MeOH (5.4 mL) was added copper sulfate pentahydrate (24.1 mg, 0.10 mmol). The reaction mixture was stirred at room temperature for 16 hours. After 16 hours, to the solution was added acetic acid (0.24 mL, 4.0 mmol), copper powder (25.5 mg, 0.40 mmol), copper sulfate (10% w/v in water, 1.6 mL), MeTHF (0.8 mL), and cyclopropylacetylene (26.5 mg, 0.4 mmol). The reaction mixture was stirred at room temperature for 3 hours, then diluted with water and MeTHF. The organic layer was isolated, filtered, concentrated *in vacuo* and purified

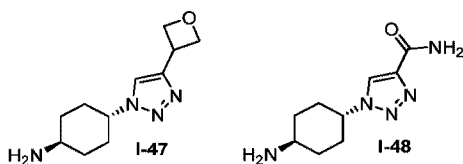
by silica gel column chromatography (eluent: EtOAc/Hex) to provide benzyl ((1*r*,4*r*)-4-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)cyclohexyl)carbamate.

ES/MS: 340.4 [M+H<sup>+</sup>].

**(1*r*,4*r*)-4-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)cyclohexan-1-amine (I-46):** To a solution of benzyl ((1*r*,4*r*)-4-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)cyclohexyl)carbamate (93.4 mg, 0.27 mmol) in EtOH (4.0 mL) was added Pd/C (29.2 mg, 0.027 mmol). The reaction flask was subjected to vacuum and backflushed with hydrogen gas three times. The reaction was maintained under a hydrogen atmosphere for 3 hours. The reaction mixture was filtered through a pad of Celite and concentrated to provide **I-46** which was used without purification.

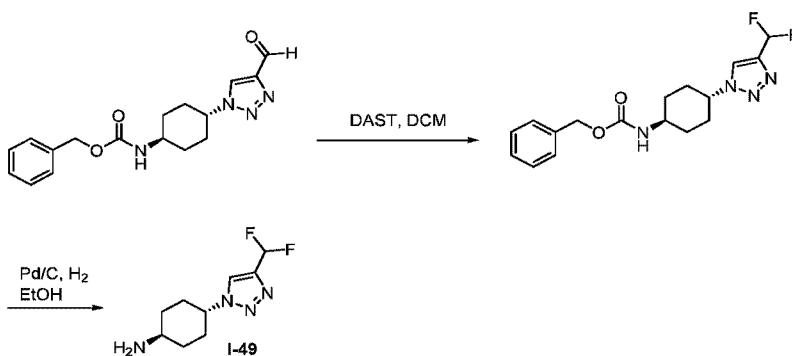
10 ES/MS: 207.0 [M+H<sup>+</sup>].

#### Preparation of Intermediates I-47 and I-48:



Intermediates **I-47** and **I-48** was prepared in the manner described for **I-46** substituting cyclopropylacetylene with 3-ethynyloxetane and propiolamide respectively.

#### 15 Preparation of Intermediate I-49:



#### **benzyl ((1*r*,4*r*)-4-(4-(difluoromethyl)-1*H*-1,2,3-triazol-1-yl)cyclohexyl)carbamate:**

To a solution of benzyl ((1*r*,4*r*)-4-(4-formyl-1*H*-1,2,3-triazol-1-yl)cyclohexyl)carbamate (obtained as described in **Preparation of Intermediate I-46** substituting propynal for cyclopropylacetylene) (200 mg, 0.61 mmol) in DCM (3.0 mL) was added DAST (169  $\mu$ L, 1.28 mmol). The reaction mixture was stirred at room temperature for one hour, then quenched by the dropwise addition of saturated aqueous sodium bicarbonate. The organic layer was isolated,

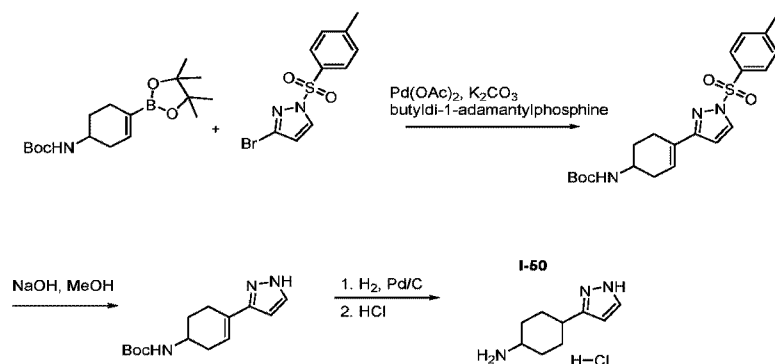
concentrated *in vacuo* and purified by silica gel column chromatography (eluent: EtOAc/Hex) to provide benzyl ((1*r*,4*r*)-4-(4-(difluoromethyl)-1*H*-1,2,3-triazol-1-yl)cyclohexyl)carbamate.

ES/MS: 351.2 [M+H<sup>+</sup>].

**(1*r*,4*r*)-4-(4-(difluoromethyl)-1*H*-1,2,3-triazol-1-yl)cyclohexan-1-amine (I-49):** To a solution of benzyl ((1*r*,4*r*)-4-(4-(difluoromethyl)-1*H*-1,2,3-triazol-1-yl)cyclohexyl)carbamate (105 mg, 0.30 mmol) in EtOH (5.0 mL) was added Pd/C (15.8 mg, 0.015 mmol). The reaction flask was subjected to vacuum and backflushed with hydrogen gas three times. The reaction was maintained under a hydrogen atmosphere for 3 hours. The reaction mixture was filtered through a pad of Celite and concentrated to provide **I-49** which was used without purification.

ES/MS: 216.2 [M+H<sup>+</sup>].

#### Preparation of Intermediate I-50:



**tert-butyl (4-(1-tosyl-1*H*-pyrazol-3-yl)cyclohex-3-en-1-yl)carbamate:** A suspension of tert-butyl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl)carbamate (450 mg, 1.392 mmol), 3-bromo-1-tosyl-1*H*-pyrazole (500 mg, 1.660 mmol), Palladium acetate (16 mg, 0.071 mmol), Butyl-di-1-adamantylphosphine min. 95% (53 mg, 0.148 mmol), and Potassium carbonate (385 mg, 12.786 mmol) in DME (8 mL) and water (4 mL) was degassed for 10 min with argon, then heated at 80 deg o/n. The reaction was diluted with EtOAc, washed with brine, and dried over sodium sulfate. Chromatographed (eluent: EtOAc/hexanes) gave product tert-butyl (4-(1-tosyl-1*H*-pyrazol-3-yl)cyclohex-3-en-1-yl)carbamate.

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 2.8 Hz, 1H), 7.96 – 7.86 (m, 2H), 7.52 (d, *J* = 2.4 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 6.45 (d, *J* = 2.8 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 6.29 – 6.19 (m, 1H), 4.58 (s, 1H), 3.86 (s, 1H), 2.73 – 2.44 (m, 3H), 2.44 (s, 3H), 2.18 – 2.02 (m, 1H), 2.02 – 1.83 (m, 1H), 1.78 – 1.57 (m, 1H), 1.46 (s, 9H).

ES/MS: 417.2 (M+H<sup>+</sup>).

**tert-butyl (4-(1H-pyrazol-3-yl)cyclohex-3-en-1-yl)carbamate:** A suspension of tert-butyl (4-(1-tosyl-1H-pyrazol-3-yl)cyclohex-3-en-1-yl)carbamate (0.345 g, 0.826 mmol) and Sodium Hydroxide (184 mg, 4.6 mmol) in MeOH (5 mL) was stirred at rt for 4 hr. The reaction was concentrated to dryness, then diluted with EtOAc, neutralized with 1N HCl (5 mL), and  
5 dried over sodium sulfate to give product tert-butyl (4-(1H-pyrazol-3-yl)cyclohex-3-en-1-yl)carbamate.

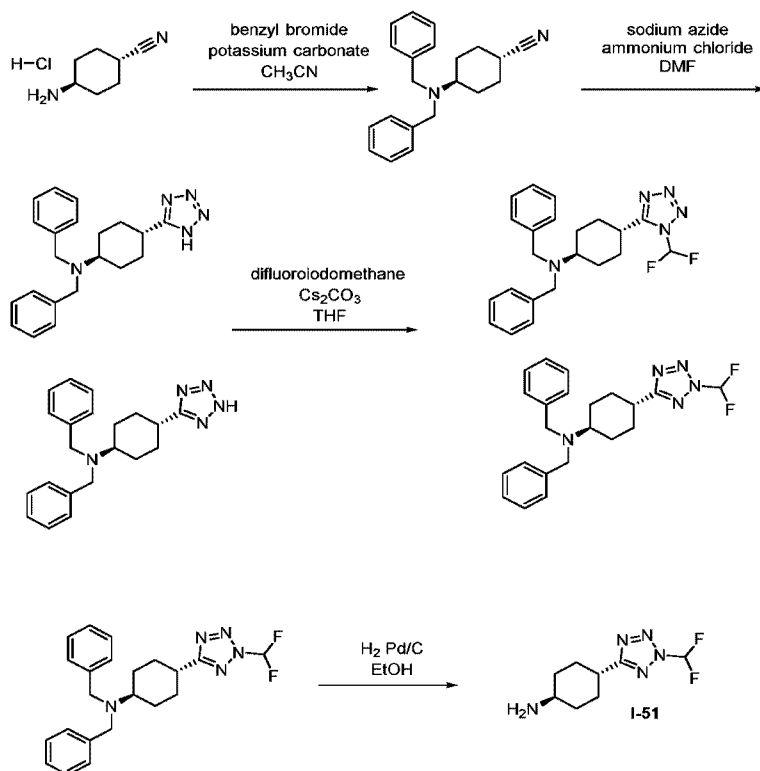
<sup>1</sup>H NMR (400 MHz, Chloroform-d)  $\delta$  9.19 (s, 2H), 7.57 (d, J = 2.3 Hz, 1H), 6.37 (d, J = 2.4 Hz, 1H), 6.31 – 6.12 (m, 1H), 4.65 (s, 0H), 3.92 – 3.66 (m, 1H), 2.85 – 2.44 (m, 2H), 2.18 – 1.88 (m, 2H), 1.85 – 1.53 (m, 1H), 1.47 (s, 6H), 1.35 – 1.11 (m, 1H), 0.97 – 0.74 (m, 0H).

10 ES/MS: 263.8 (M+H<sup>+</sup>).

**(1r,4r)-4-(2-(difluoromethyl)-2H-tetrazol-5-yl)cyclohexan-1-amine (I-50):** A solution of tert-butyl (4-(1H-pyrazol-3-yl)cyclohex-3-en-1-yl)carbamate (0.315 g, 1.2 mmol) in EtOH (25 mL) was degassed with argon and vacuum. Pd/C (10%, 64 mg, 0.06 mmol) was added and the mixture was stirred with a balloon of H<sub>2</sub> overnight. The reaction was filtered over a  
15 Celite plug, rinsed with EtOAc and the filtrate was concentrated to give 183 mg of tert-butyl (4-(1H-pyrazol-3-yl)cyclohexyl)carbamate.

ES/MS: 266 (M+H<sup>+</sup>).

To a solution of tert-butyl (4-(1H-pyrazol-3-yl)cyclohexyl)carbamate (183 mg, 0.690 mmol) in DCM (8 mL) was added HCl (4.0M in dioxane, 1.1 mL, 4.4 mmol) and the resulting  
20 solution stirred at room temperature overnight. Upon completion, the reaction mixture was concentrated to dryness to give 4-(1H-pyrazol-3-yl)cyclohexan-1-amine hydrochloride (**I-50**) which was used without further purification.

**Preparation of Intermediate I-51:**

**(1r,4r)-4-(dibenzylamino)cyclohexane-1-carbonitrile:** To a solution of 4-aminocyclohexanecarbonitrile hydrochloride (977 mg, 6.08 mmol) and potassium carbonate (3362.09 mg, 24.33 mmol) in CH<sub>3</sub>CN (15 mL), was added benzyl bromide (1800  $\mu$ l, 15.13 mmol). The reaction was heated at 80 deg o/n. The reaction mixture was filtered and the filtrate was diluted with EtOAc and brine. The organic extract was dried over sodium sulfate and chromatographed (eluent EtOAc/hexanes to give product (1r,4r)-N,N-dibenzyl-4-(1H-tetrazol-5-yl)cyclohexan-1-amine.

<sup>1</sup>H NMR (400 MHz, Chloroform-d)  $\delta$  7.49 – 7.33 (m, 9H), 7.30 (dq, J = 5.4, 1.9 Hz, 2H), 3.67 (d, J = 3.4 Hz, 4H), 2.59 (tt, J = 11.5, 3.5 Hz, 1H), 2.42 – 2.27 (m, 1H), 2.20 (dt, J = 12.6, 2.9 Hz, 3H), 2.14 – 1.98 (m, 3H), 1.47 (dq, J = 48.7, 13.0, 3.3 Hz, 6H).

(M+H<sup>+</sup>) 305.3

**(1r,4r)-N,N-dibenzyl-4-(1H-tetrazol-5-yl)cyclohexan-1-amine:** To a solution of tert-butyl N-(4-cyanocyclohexyl)carbamate (1431 mg, 4.70 mmol) in DMF (15 mL), was added sodium azide (1080 mg, 16.46 mmol) and ammonium chloride (880 mg, 16.45 mmol). The reaction was heated at 120 deg for 48 hr. The reaction mixture was diluted with EtOAc and washed with LiCl 5% solution 3x. The organic extract was dried over sodium sulfate and

chromatographed (eluent EtOAc/hexanes) to give a tautomeric mixture of products (1r,4r)-N,N-dibenzyl-4-(1H-tetrazol-5-yl)cyclohexan-1-amine and (1r,4r)-N,N-dibenzyl-4-(2H-tetrazol-5-yl)cyclohexan-1-amine.

1H NMR (400 MHz, Chloroform-d)  $\delta$  7.44 – 7.33 (m, 4H), 7.33 – 7.26 (m, 5H), 7.26 – 7.18 (m, 2H), 7.00 (s, 3H), 3.76 (s, 4H), 3.00 (s, 2H), 2.91 (s, 1H), 2.77 (s, 1H), 2.16 (dd, J = 53.1, 7.7 Hz, 5H), 1.71 – 1.49 (m, 4H).

(M+H<sup>+</sup>) 348.2

**(1r,4r)-N,N-dibenzyl-4-(2-(difluoromethyl)-2H-tetrazol-5-yl)cyclohexan-1-amine:** In a 40 mL reaction vial containing a tautomeric mixture of (1r,4r)-N,N-dibenzyl-4-(1H-tetrazol-5-yl)cyclohexan-1-amine and (1r,4r)-N,N-dibenzyl-4-(2H-tetrazol-5-yl)cyclohexan-1-amine and cesium carbonate (1077 mg, 3.31 mmol), was added difluoroiodomethane (8.0 ml, 4 mmol, 10% wt. in THF). The suspension was heated at 40 deg o/n. The reaction was diluted with EtOAc and washed with brine. The organic extract was dried over sodium sulfate and chromatographed (eluent EtOAc/hexanes) to give a major product (1r,4r)-N,N-dibenzyl-4-(2-(difluoromethyl)-2H-tetrazol-5-yl)cyclohexan-1-amine and minor product (1r,4r)-N,N-dibenzyl-4-(1-(difluoromethyl)-1H-tetrazol-5-yl)cyclohexan-1-amine.

1H NMR (400 MHz, Chloroform-d)  $\delta$  7.58 (d, J = 57.9 Hz, 1H), 7.43 – 7.37 (m, 4H), 7.36 – 7.30 (m, 4H), 7.28 – 7.22 (m, 2H), 3.69 (s, 4H), 3.05 (ddd, J = 12.5, 9.3, 3.5 Hz, 1H), 2.81 – 2.61 (m, 1H), 2.11 (dt, J = 13.1, 2.9 Hz, 4H), 1.77 (td, J = 14.0, 11.0 Hz, 2H), 1.64 – 1.49 (m, 2H).

(M+H<sup>+</sup>) 398.4

**(1r,4r)-4-(2-(difluoromethyl)-2H-tetrazol-5-yl)cyclohexan-1-amine (I-51):** A suspension of (1r,4r)-N,N-dibenzyl-4-(2-(difluoromethyl)-2H-tetrazol-5-yl)cyclohexan-1-amine (392.5 mg, 0.987 mmol) in EtOH (20 mL) was degassed with argon. Pd/C (10%, 52 mg, 0.049 mmol) was added and purged once more with argon and stirred with a balloon of hydrogen at rt overnight. The suspension was filtered through a fritted funnel with Celite and concentrated to give product (1r,4r)-4-(2-(difluoromethyl)-2H-tetrazol-5-yl)cyclohexan-1-amine (**I-51**), which was used without further purification.

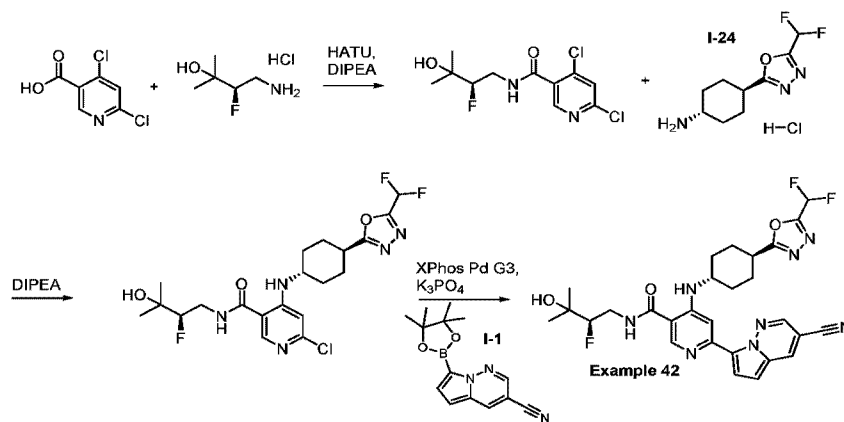
1H NMR (400 MHz, Chloroform-d)  $\delta$  7.67 (t, J = 58.0 Hz, 1H), 3.07 (tt, J = 12.2, 3.4 Hz, 1H), 2.85 (tt, J = 11.3, 3.7 Hz, 1H), 2.07 (dtd, J = 12.7, 7.1, 6.1, 3.2 Hz, 4H), 1.89 (qd, J = 14.2, 13.4, 3.5 Hz, 2H), 1.53 (s, 2H), 1.37 – 1.21 (m, 2H).

(M+H<sup>+</sup>) 218.0

## EXAMPLE PROCEDURES AND COMPOUND EXAMPLES

### Procedure 1: Example 42:

**6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1*r*,4*R*)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexyl)amino)-*N*-((*R*)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide**  
**(Example 42)**



**(*R*)-6-bromo-4-chloro-*N*-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide.** To a solution of 6-bromo-4-chloronicotinic acid (3 g, 12.69 mmol) in DMF (42 mL) was added HATU (6.27 g, 16.49 mmol), (*R*)-4-amino-3-fluoro-2-methylbutan-2-ol hydrochloride (2.4 g, 15.23 mmol), and *N,N*-Diisopropylethylamine (5.62 ml, 32.26 mmol). The resulting solution was stirred at room temperature overnight and subsequently diluted with ethyl acetate. The organic solution was washed with saturated aqueous lithium chloride (3 times), then dried over  $\text{Na}_2\text{SO}_4$ , and then concentrated. The residue was purified by silica gel chromatography (eluent: EtOAc/hexanes) to provide (*R*)-6-bromo-4-chloro-*N*-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide.

ES/MS: 341.1 ( $\text{M}+\text{H}^+$ ).

**6-chloro-4-(((1*r*,4*R*)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexyl)amino)-*N*-((*R*)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide:** (*R*)-4,6-dichloro-*N*-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (0.23 g, 0.78 mmol) and (1*r*,4*r*)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexan-1-amine hydrochloride **I-24** (0.26 g, 1.00 mmol) were added to a microwave vial followed by NMP (4 mL) and diisopropylethylamine (0.68 mL, 3.90 mmol). The resulting solution was heated to 160 °C in a microwave reactor for 45 min. The reaction mixture was then poured into water (8 mL) and extracted with EtOAc (2 x 30 mL). The organic layers were then combined, dried over  $\text{MgSO}_4$ , filtered and concentrated with the resulting crude residue then purified via silica gel chromatography (eluent: EtOAc/hexanes/MeOH) to give the

desired product. Note: In some instances, heating to 160 °C in a microwave reactor for up to 8 hours is necessary.

ES/MS: 477.0 (M+H<sup>+</sup>).

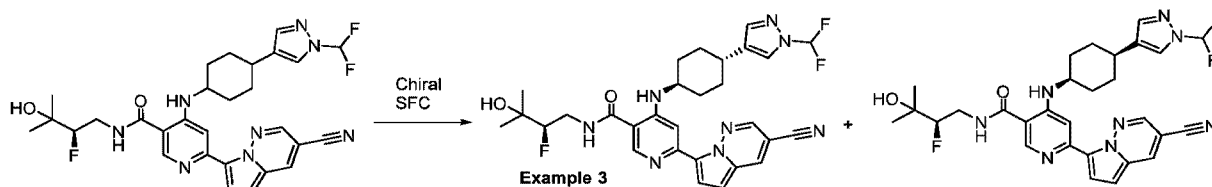
**6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (Example 42):** 6-chloro-4-(((1r,4R)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (0.21 g, 0.44 mmol) and 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[1,2-b]pyridazine-3-carbonitrile (0.17 g, 0.62 mmol) were added to a microwave vial followed by DME (3.5 mL), XPhos Pd G3 (37 mg, 0.044 mmol) and K<sub>3</sub>PO<sub>4</sub> (0.5M in water, 1.3 mL, 0.66 mmol). The resulting mixture was purged with argon for 2 minutes, sealed and heated to 120 °C in a microwave reactor for 10 min. The reaction mixture was filtered and purified by RP-HPLC (eluent: water / MeCN \*0.1% TFA). The product fractions were combined and lyophilized to give the final product as a TFA salt.

ES/MS: 583.4 (M+H<sup>+</sup>).

<sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) δ 8.75 (d, J = 2.2 Hz, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.58 (s, 1H), 8.03 (d, J = 5.0 Hz, 1H), 7.91 (s, 1H), 7.21 (d, J = 5.1 Hz, 1H), 7.14 (t, J = 51.6 Hz, 1H), 4.42 (ddd, J = 49.0, 9.4, 2.1 Hz, 1H), 4.12 - 3.79 (m, 2H), 3.63 - 3.41 (m, 1H), 3.26 - 3.12 (m, 1H), 2.47 - 2.20 (m, 4H), 2.04 - 1.84 (m, 2H), 1.76 - 1.60 (m, 2H), 1.29 (d, J = 1.6 Hz, 6H).

### Procedure 2: Example 3:

**6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-(difluoromethyl)-1H-pyrazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (Example 3)**



**6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-(difluoromethyl)-1H-pyrazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (Example 3):**

(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-(difluoromethyl)-1H-pyrazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (obtained as

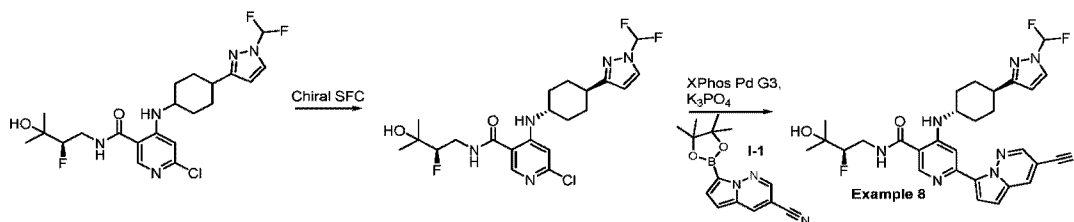
described in **Procedure 1** substituting (1*r*,4*r*)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexan-1-amine hydrochloride with 4-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)cyclohexan-1-amine hydrochloride (**I-2**) was separated by reverse phase high pressure liquid chromatography (SFC IA, eluent: SFC/EtOH) to provide the final compound.

5 ES/MS: 581.2 [M+H<sup>+</sup>].

<sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 8.61 - 8.57 (m, 2H), 8.55 (d, *J* = 2.2 Hz, 1H), 8.24 (s, 1H), 7.96 (s, 1H), 7.83 (d, *J* = 4.8 Hz, 1H), 7.72 (s, 1H), 7.43 (t, *J* = 59.9 Hz, 1H), 7.11 (d, *J* = 4.9 Hz, 1H), 4.45 (ddd, *J* = 49.0, 9.1, 2.2 Hz, 1H), 3.90 (ddd, *J* = 35.6, 14.5, 2.3 Hz, 1H), 3.70 - 3.58 (m, 1H), 3.57 - 3.41 (m, 1H), 2.70 (t, *J* = 11.8 Hz, 1H), 2.36 (d, *J* = 12.4 Hz, 2H), 2.18 (d, *J* = 13.2 Hz, 2H), 1.69 (q, *J* = 11.5 Hz, 2H), 1.61 - 1.44 (m, 2H), 1.32 (d, *J* = 1.7 Hz, 6H).

### Procedure 3: Example 8:

**6-(3-cyanopyrrolo[1,2-*b*]pyridazin-7-yl)-4-(((1*r*,4*R*)-4-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)cyclohexyl)amino)-N-((*R*)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (Example 8)**



15

**6-(3-cyanopyrrolo[1,2-*b*]pyridazin-7-yl)-4-(((1*r*,4*R*)-4-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)cyclohexyl)amino)-N-((*R*)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (Example 8):** (*R*)-6-chloro-4-((4-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)cyclohexyl)amino)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (obtained in the manner described in **Procedure**

20 **1** substituting (1*r*,4*r*)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexan-1-amine hydrochloride **I-24** with 4-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)cyclohexan-1-amine hydrochloride **I-13**) was purified by chiral SFC on an SFC-ID column with SFC 70% EtOH-TFA as co-solvent to deliver pure 6-chloro-4-(((1*r*,4*R*)-4-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)cyclohexyl)amino)-N-((*R*)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide which was

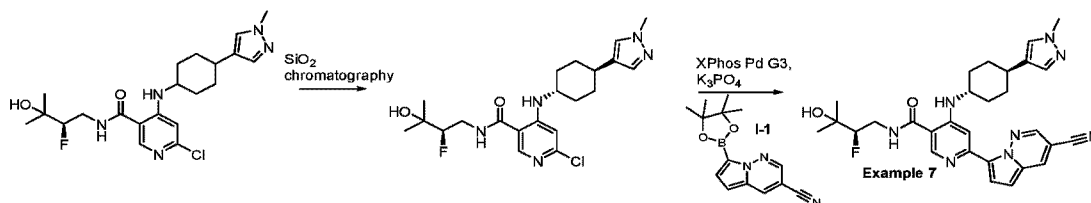
25 elaborated to the final compound 6-(3-cyanopyrrolo[1,2-*b*]pyridazin-7-yl)-4-(((1*r*,4*R*)-4-(1-(difluoromethyl)-1*H*-pyrazol-3-yl)cyclohexyl)amino)-N-((*R*)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide **Example 8** according to the same procedure as described for step 2 of **Procedure 1**.

ES/MS: 581.4 (M+H<sup>+</sup>).

1H NMR (400 MHz, Methanol-d<sub>4</sub>)  $\delta$  8.60 (s, 1H), 8.58 (d, J = 2.3 Hz, 1H), 8.54 (d, J = 2.2 Hz, 1H), 8.25 (s, 1H), 7.96 (d, J = 2.6 Hz, 1H), 7.83 (d, J = 4.9 Hz, 1H), 7.42 (t, J = 59.9 Hz, 1H), 7.11 (d, J = 4.9 Hz, 1H), 6.48 (d, J = 2.7 Hz, 1H), 4.57 - 4.30 (m, 0H), 3.91 (d, J = 52.2 Hz, 0H), 3.37 (s, 3H), 2.83 (s, 1H), 2.37 (d, J = 12.3 Hz, 2H), 2.19 (d, J = 13.4 Hz, 2H), 1.79 (d, J = 13.4 Hz, 1H), 1.53 (d, J = 12.2 Hz, 1H), 1.32 (d, J = 1.7 Hz, 6H).

**Procedure 4: Example 7:**

**6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(1-methyl-1H-pyrazol-4-yl)cyclohexyl)amino)nicotinamide (Example 7)**



10 **6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(1-methyl-1H-pyrazol-4-yl)cyclohexyl)amino)nicotinamide (Example 7):** (R)-6-chloro-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(1-methyl-1H-pyrazol-4-yl)cyclohexyl)amino)nicotinamide (synthesized according to step 1 of **Procedure 1**) was purified by silica gel chromatography (eluent EtOAc / hexanes) to deliver pure 6-chloro-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(1-methyl-1H-pyrazol-4-yl)cyclohexyl)amino)nicotinamide which was elaborated to the final compound 6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(1-methyl-1H-pyrazol-4-yl)cyclohexyl)amino)nicotinamide **Example 7** according to the same procedure as described for step 2 of **Procedure 1**.

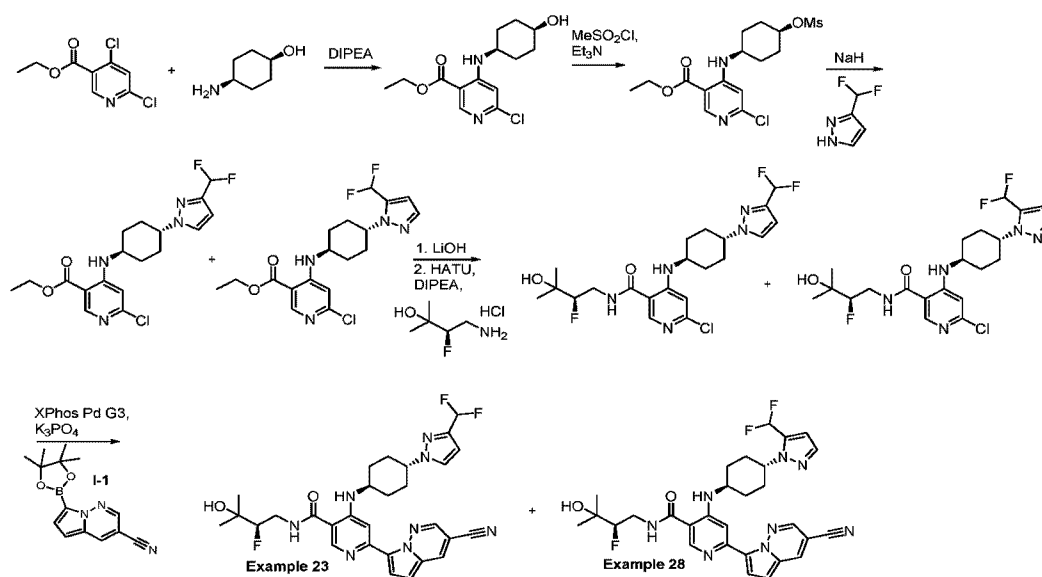
20 ES/MS: 545.3 (M+H<sup>+</sup>).

1H NMR (400 MHz, Methanol-d<sub>4</sub>)  $\delta$  9.01 (d, J = 5.9 Hz, 0H), 8.77 (d, J = 2.2 Hz, 1H), 8.69 (d, J = 2.1 Hz, 1H), 8.59 (s, 1H), 8.04 (d, J = 5.1 Hz, 1H), 7.92 (s, 1H), 7.48 (s, 1H), 7.41 (s, 1H), 7.23 (d, J = 5.1 Hz, 1H), 4.45 (ddd, J = 49.0, 9.4, 2.2 Hz, 1H), 4.12 - 3.88 (m, 1H), 3.87 (s, 3H), 3.69 - 3.41 (m, 1H), 2.72 - 2.53 (m, 0H), 2.28 (d, J = 10.9 Hz, 2H), 2.15 (d, J = 11.9 Hz, 2H), 1.65 (h, J = 12.0 Hz, 4H), 1.31 (d, J = 1.7 Hz, 6H).

**Procedure 5: Examples 23 and 28**

**6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(3-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (Example 23) and 6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(5-**

**(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (Example 28)**



**Ethyl 6-chloro-4-(((1S,4S)-4-((methylsulfonyl)oxy)cyclohexyl)amino)nicotinate: A**

5 solution of ethyl 4,6-dichloronicotinate (11.5 g, 52.3 mmol) and (1S,4S)-4-aminocyclohexan-1-ol (15.9 g, 105 mmol) in acetonitrile (120 mL) was heated at 80 °C for 16h then concentrated directly and used without further purification. The crude ethyl 6-chloro-4-(((1S,4S)-4-hydroxycyclohexyl)amino)nicotinate (14.0 g, 46.9 mmol) was then dissolved in DCM (250 mL) and triethylamine (16.3 mL, 117 mmol) after which methanesulfonyl chloride (7.25 mL, 93.7

10 mmol) was added and the resulting solution stirred for 5h at room temperature. Upon completion the reaction mixture was concentrated directly and the crude residue purified by silica gel chromatography (eluent: EtOAc/hexanes) to give ethyl 6-chloro-4-(((1S,4S)-4-((methylsulfonyl)oxy)cyclohexyl)amino)nicotinate.

ES/MS: 377.5 (M+H<sup>+</sup>).

15 **Ethyl 6-chloro-4-(((1R,4R)-4-(3-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)nicotinate and ethyl 6-chloro-4-(((1R,4R)-4-(5-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)nicotinate:** To a solution of 3-(difluoromethyl)-1H-pyrazole (0.17 g, 1.46 mmol) in DMF (4 mL) was added NaH (60% dispersion in mineral oil, 56 mg, 1.39 mmol) and the resulting suspension stirred for 10 minutes at room temperature. give ethyl 6-chloro-4-(((1S,4S)-4-((methylsulfonyl)oxy)cyclohexyl)amino)nicotinate (0.50 g, 1.33 mmol) was

20 then added and the resulting mixture heated to 100 °C for 2h. Upon completion the reaction mixture was cooled to room temperature, diluted with EtOAc (30 mL), washed with brine (5

mL), dried over MgSO<sub>4</sub>, filtered and concentrated to give a mixture of ethyl 6-chloro-4-(((1r,4r)-4-(3-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)nicotinate and ethyl 6-chloro-4-(((1r,4r)-4-(5-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)nicotinate which was used without further purification.

5           **6-chloro-4-(((1r,4R)-4-(3-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide and 6-chloro-4-(((1r,4R)-4-(5-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide:** A mixture of ethyl 6-chloro-4-(((1r,4r)-4-(3-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)nicotinate and ethyl 6-chloro-4-(((1r,4r)-4-(5-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)nicotinate (0.10 g, 0.25 mmol) was dissolved in MeOH (1 mL) and THF (1 mL) after which LiOH (2M aq., 1 mL, 2 mmol) was added and the resulting solution stirred at room temperature for 2h. Upon completion the crude reaction mixture was purified by RP-HPLC (eluent: water / MeCN \*0.1% TFA). The mixture of 6-chloro-4-(((1r,4r)-4-(3-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)nicotinic acid and 6-chloro-4-(((1r,4r)-4-(5-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)nicotinic acid (82 mg, 0.22 mmol) was then dissolved in NMP (0.5 mL) and this was followed by the sequential addition of HATU (91 mg, 0.24 mmol) and triethylamine (0.2 mL). After 20 minutes stirring at room temperature (R)-4-amino-3-fluoro-2-methylbutan-2-ol hydrochloride (70 mg, 0.44 mmol) was added and the resulting reaction mixture stirred for 30 minutes. Upon completion the reaction mixture was diluted with EtOAc (20 mL), washed with saturated aqueous NaHCO<sub>3</sub> (5 mL) then brine (5 mL), dried and concentrated to give a mixture of 6-chloro-4-(((1r,4R)-4-(3-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide and 6-chloro-4-(((1r,4R)-4-(5-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide which was used without further purification.

ES/MS: 474.2 (M+H<sup>+</sup>).

30           **6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(3-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (Example 23) and 6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(5-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (Example 28):** 6-chloro-4-(((1r,4R)-4-(3-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide and 6-chloro-4-(((1r,4R)-4-(5-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (0.10 g, 0.21 mmol) and 7-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)pyrrolo[1,2-b]pyridazine-3-carbonitrile (0.11 g, 0.42 mmol) were added to a microwave vial followed by DME (1 mL), XPhos Pd G3 (18 mg, 0.021 mmol) and K<sub>3</sub>PO<sub>4</sub> (2M in water, 0.21 mL, 0.42 mmol). The resulting mixture was purged with argon for 2 minutes, sealed and heated to 120 °C in a microwave reactor for 20 min. The reaction mixture was  
 5 filtered and purified by RP-HPLC (eluent: water / MeCN \*0.1% TFA). The mixture of 6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(3-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide and 6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(5-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide was separated by  
 10 chiral SFC on an SFC IE column with SFC 80%EtOH-TFA as co-solvent.

**6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(3-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (Example 23)**

ES/MS: 581.6 (M+H<sup>+</sup>).

15 <sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) δ 8.68 (d, J = 2.1 Hz, 1H), 8.59 (d, J = 1.7 Hz, 1H), 8.05 (dd, J = 5.1, 1.7 Hz, 1H), 7.94 (d, J = 1.7 Hz, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.21 (dd, J = 5.2, 1.6 Hz, 1H), 6.73 (td, J = 55.1, 1.7 Hz, 1H), 6.49 (d, J = 2.7 Hz, 1H), 4.58 - 4.26 (m, 2H), 4.08 - 3.80 (m, 2H), 3.61 - 3.42 (m, 1H), 2.39 - 2.30 (m, 2H), 2.25 (d, J = 11.0 Hz, 2H), 2.19 - 2.03 (m, 2H), 1.71 (qd, J = 12.9, 3.5 Hz, 2H), 1.29 (d, J = 1.7 Hz, 6H).

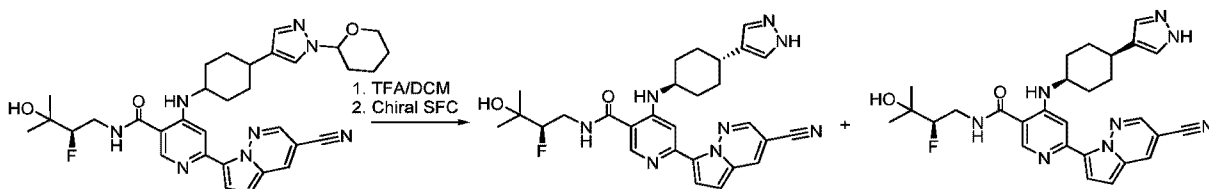
20 **6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(5-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (Example 28)**

ES/MS: 581.3 (M+H<sup>+</sup>).

25 <sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) δ 8.75 (d, J = 2.3 Hz, 1H), 8.69 (d, J = 2.3 Hz, 1H), 8.58 (s, 1H), 8.06 (d, J = 5.0 Hz, 1H), 7.98 (s, 1H), 7.58 (d, J = 1.8 Hz, 1H), 7.33 - 6.89 (m, 2H), 6.63 - 6.52 (m, 1H), 4.57 - 4.30 (m, 2H), 4.07 - 3.82 (m, 2H), 3.65 - 3.43 (m, 1H), 2.47 - 2.21 (m, 4H), 2.13 (d, J = 13.0 Hz, 2H), 1.71 (q, J = 12.4 Hz, 2H), 1.29 (d, J = 1.7 Hz, 6H).

**Procedure 6: Examples 1 and 2**

30 **4-(((1r,4R)-4-(1H-pyrazol-4-yl)cyclohexyl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (Example 1) and 4-(((1s,4S)-4-(1H-pyrazol-4-yl)cyclohexyl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (Example 2):**



4-(((1*r*,4*R*)-4-(1*H*-pyrazol-4-yl)cyclohexyl)amino)-6-(3-cyanopyrrolo[1,2-  
**b**]pyridazin-7-yl)-*N*-((*R*)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (Example 1) and  
 5 4-(((1*s*,4*S*)-4-(1*H*-pyrazol-4-yl)cyclohexyl)amino)-6-(3-cyanopyrrolo[1,2-**b**]pyridazin-7-yl)-  
*N*-((*R*)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (Example 2):

To a solution of 6-(3-cyanopyrrolo[1,2-*b*]pyridazin-7-yl)-*N*-((*R*)-2-fluoro-3-hydroxy-3-  
 methylbutyl)-4-((4-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-  
 10 (5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexan-1-amine hydrochloride with 4-(1-  
 (tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)cyclohexan-1-amine hydrochloride (**I-44**) in DCM  
 (5 mL), was added TFA (0.2 mL). The reaction was stirred at room temperature overnight. The  
 reaction was concentrated and purified by RP-HPLC (eluent: water / MeCN \*0.1% TFA). The  
 product fractions were combined, lyophilized, and further separated by chiral RP-HPLC (SFC  
 15 ODH, eluent: SFC/*i*PrOH) to provide the final compounds.

#### Example 1:

ES/MS: 531.3 [*M*+*H*<sup>+</sup>].

<sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 8.77 (d, *J* = 2.1 Hz, 1H), 8.69 (d, *J* = 2.2 Hz, 1H),  
 8.60 (s, 1H), 8.05 (d, *J* = 5.1 Hz, 1H), 7.93 (s, 1H), 7.57 (s, 2H), 7.23 (d, *J* = 5.0 Hz, 1H), 4.45  
 20 (ddd, *J* = 49.1, 9.4, 2.1 Hz, 1H), 4.10 - 3.85 (m, 2H), 3.52 (ddd, *J* = 16.0, 14.5, 9.4 Hz, 1H), 2.71  
 (t, *J* = 11.5 Hz, 1H), 2.38 - 2.23 (m, 2H), 2.24 - 2.05 (m, 2H), 1.89 - 1.52 (m, 4H), 1.32 (d, *J* =  
 1.7 Hz, 6H), 0.97 - 0.78 (m, 1H).

<sup>19</sup>F NMR (376 MHz, Methanol-*d*<sub>4</sub>) δ -77.56, -195.84 (ddd, *J* = 50.7, 36.4, 16.0 Hz).

#### Example 2:

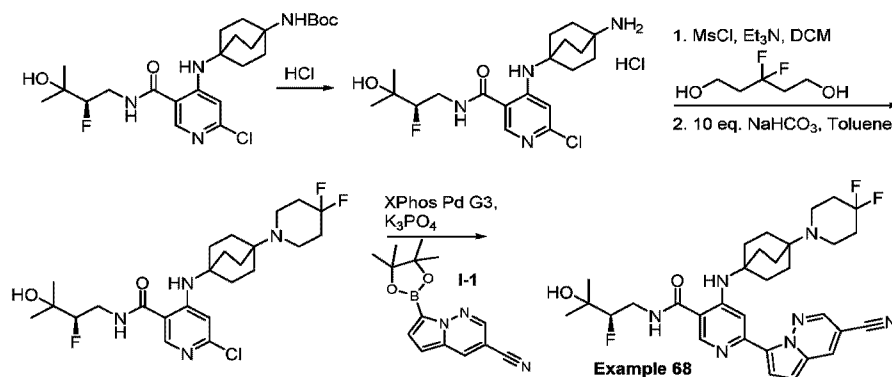
25 ES/MS: 531.3 [*M*+*H*<sup>+</sup>].

<sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 8.78 (d, *J* = 2.2 Hz, 1H), 8.69 (d, *J* = 2.2 Hz, 1H),  
 8.63 (s, 1H), 8.03 (d, *J* = 5.1 Hz, 1H), 7.90 (s, 1H), 7.56 (s, 2H), 7.24 (d, *J* = 5.0 Hz, 1H), 4.45  
 (ddd, *J* = 49.1, 9.4, 2.2 Hz, 1H), 4.26 (s, 1H), 3.96 (ddd, *J* = 36.5, 14.5, 2.2 Hz, 1H), 3.56 - 3.42

(m, 1H), 2.82 (t, J = 10.5 Hz, 1H), 2.03 (d, J = 11.0 Hz, 7H), 1.77 (d, J = 11.4 Hz, 2H), 1.31 (d, J = 1.7 Hz, 6H), 0.97 - 0.82 (m, 1H).

### Procedure 7: Example 68

**(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-((4-(4,4-difluoropiperidin-1-yl)bicyclo[2.2.2]octan-1-yl)amino)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide**  
 5 **(Example 68)**



**(R)-4-((4-aminobicyclo[2.2.2]octan-1-yl)amino)-6-chloro-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide hydrochloride:** tert-butyl (R)-4-((2-chloro-5-((2-fluoro-3-hydroxy-3-methylbutyl)carbamoyl)pyridin-4-yl)amino)bicyclo[2.2.2]octan-1-yl)carbamate (0.35 g, 0.70 mmol) (obtained in the manner described in step 1 of **Procedure 1** substituting (1*r*,4*r*)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexan-1-amine hydrochloride **I-24** with tert-butyl (4-aminobicyclo[2.2.2]octan-1-yl)carbamate hydrochloride) was dissolved in HCl solution (4.0M in dioxane, 3 mL, 12 mmol) and stirred for 3h at room temperature. Upon completion the  
 10 reaction mixture was concentrated to dryness to give (R)-4-((4-aminobicyclo[2.2.2]octan-1-yl)amino)-6-chloro-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide hydrochloride which was used without further purification.  
 15

**(R)-6-chloro-4-((4-(4,4-difluoropiperidin-1-yl)bicyclo[2.2.2]octan-1-yl)amino)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide:** To a solution of 3,3-difluoropentane-1,5-diol (100 mg, 0.71 mmol) and triethylamine (0.5 mL, 3.5 mmol) in 2 mL of DCM, methanesulfonyl chloride (0.17 mL, 2.1 mmol) was added to the solution. It was stirred for overnight. Diluted with 30 mL of ethylacetate and washed with NaHCO<sub>3</sub> and brine. The organic layer was dried and concentrated. Used without further purification. The crude product and (R)-4-((4-aminobicyclo[2.2.2]octan-1-yl)amino)-6-chloro-N-(2-fluoro-3-hydroxy-3-  
 20 methylbutyl)nicotinamide hydrochloride (100 mg, 0.23 mmol) were dissolved in toluene (3 mL), powder of NaHCO<sub>3</sub> (143 mg, 2.3 mmol) was added to the solution. It was heated to 110 °C for

16 hours. Removed the solvent and the crude residue purified on HPLC prep (eluent: 10% to 50% of water / MeCN \*0.1% TFA) to give (R)-6-chloro-4-(((4-(4,4-difluoropiperidin-1-yl)bicyclo[2.2.2]octan-1-yl)amino)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide.

ES/MS: 503.5 (M+H+).

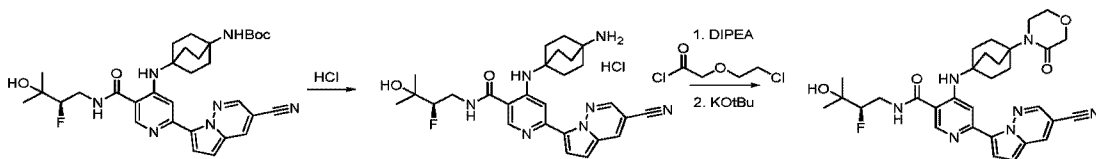
5 **(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((4-(4,4-difluoropiperidin-1-yl)bicyclo[2.2.2]octan-1-yl)amino)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide**  
**(Example 68):** (R)-6-chloro-4-(((4-(4,4-difluoropiperidin-1-yl)bicyclo[2.2.2]octan-1-yl)amino)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide was converted to the final product (R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((4-(4,4-difluoropiperidin-1-yl)bicyclo[2.2.2]octan-1-yl)amino)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide **(Example 68)** in the manner described in step 2 of **Procedure 1** substituting 6-chloro-4-(((1r,4R)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide with (R)-6-chloro-4-(((4-(4,4-difluoropiperidin-1-yl)bicyclo[2.2.2]octan-1-yl)amino)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide.

15 ES/MS: 610.4 [M+H<sup>+</sup>].

<sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) δ 8.76 (s, 2H), 8.60 (s, 1H), 8.33 (s, 1H), 7.95 (d, J = 5.1 Hz, 1H), 7.22 (d, J = 5.0 Hz, 1H), 4.40 (ddd, J = 49.1, 9.4, 2.1 Hz, 1H), 4.05 - 3.33 (m, 5H), 2.42 (d, J = 12.5 Hz, 4H), 2.33 (dd, J = 10.0, 5.0 Hz, 6H), 2.22 (dd, J = 9.9, 5.1 Hz, 6H), 1.28 (d, J = 1.7 Hz, 6H).

20 **Procedure 8: Example 69**

**(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-(2-fluoro-3-hydroxy-3-methylbutyl)-4-(((4-(3-oxomorpholino)bicyclo[2.2.2]octan-1-yl)amino)nicotinamide** **(Example 69)**



25 **(R)-4-(((4-aminobicyclo[2.2.2]octan-1-yl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide hydrochloride:** tert-butyl (R)-4-(((2-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-5-((2-fluoro-3-hydroxy-3-methylbutyl)carbamoyl)pyridin-4-yl)amino)bicyclo[2.2.2]octan-1-yl)carbamate (0.14 g, 0.23 mmol) (obtained in the manner described in **Procedure 1** substituting (1r,4r)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexan-1-amine hydrochloride **I-24** with tert-butyl  
 30 (4-aminobicyclo[2.2.2]octan-1-yl)carbamate hydrochloride) was dissolved in HCl solution

(4.0M in dioxane, 2 mL, 8 mmol) and stirred for 2h at room temperature. Upon completion the reaction mixture was concentrated to dryness to give (R)-4-((4-aminobicyclo[2.2.2]octan-1-yl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide hydrochloride which was used without further purification.

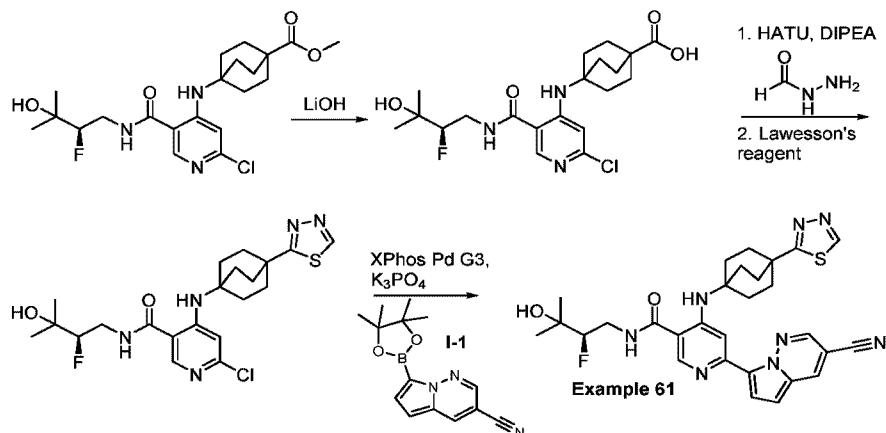
5           **(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-(2-fluoro-3-hydroxy-3-methylbutyl)-4-((4-(3-oxomorpholino)bicyclo[2.2.2]octan-1-yl)amino)nicotinamide (Example 69):** To a suspension of (R)-4-((4-aminobicyclo[2.2.2]octan-1-yl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide hydrochloride (80 mg, 0.15 mmol) and diisopropylethylamine (0.13 mL, 0.74 mmol) in 3 mL of acetonitrile and 1 mL  
10 of DMF, 2-(2-chloroethoxy)acetyl chloride (46.4 mg, 0.3 mmol) was added to the solution. Then it was stirred for 1 hour, diluted with 30 mL of ethyl acetate and washed with 10 mL of sodium bicarbonate solution and 10 mL of brine. The organic was concentrated. The crude product was dissolved in THF, 1N of potassium tert-butoxide (0.58 mL, 0.58 mmol) was added to the  
15 solution. It was stirred for 10 minutes. Acidified by 1 N HCl and removed the solvent. The mixture was purified by HPLC prep (eluent: 10% to 50% of water / MeCN \*0.1% TFA) to give (R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-(2-fluoro-3-hydroxy-3-methylbutyl)-4-((4-(3-oxomorpholino)bicyclo[2.2.2]octan-1-yl)amino)nicotinamide (**Example 69**).

ES/MS: 590.7 (M+H<sup>+</sup>).

1H NMR (400 MHz, Methanol-d<sub>4</sub>) δ 8.76 (t, J = 1.5 Hz, 2H), 8.54 (s, 1H), 8.41 (s, 1H),  
20 7.92 (d, J = 5.1 Hz, 1H), 7.22 (d, J = 5.1 Hz, 1H), 4.40 (ddd, J = 49.0, 9.4, 2.1 Hz, 1H), 4.05 (s, 2H), 4.00 - 3.87 (m, 1H), 3.83 (dd, J = 6.0, 4.1 Hz, 2H), 3.57 - 3.42 (m, 3H), 2.40 (dd, J = 10.3, 5.3 Hz, 6H), 2.24 (dd, J = 10.3, 5.4 Hz, 6H), 1.28 (d, J = 1.7 Hz, 6H).

**Procedure 9: Example 61**

**(R)-4-((4-(1,3,4-thiadiazol-2-yl)bicyclo[2.2.2]octan-1-yl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (Example 61)**



5

**(R)-4-((2-chloro-5-((2-fluoro-3-hydroxy-3-methylbutyl)carbamoyl)pyridin-4-yl)amino)bicyclo[2.2.2]octane-1-carboxylic acid:** methyl (R)-4-((2-chloro-5-((2-fluoro-3-hydroxy-3-methylbutyl)carbamoyl)pyridin-4-yl)amino)bicyclo[2.2.2]octane-1-carboxylate (0.80 g, 1.81 mmol) (obtained in the manner described in **Procedure 1** substituting (1*r*,4*r*)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexan-1-amine hydrochloride **I-24** with methyl 4-aminobicyclo[2.2.2]octane-1-carboxylate hydrochloride) was dissolved in MeOH (1 mL) and THF (1 mL) after which LiOH (2M aq., 1.5 mL, 3 mmol) was added and the resulting reaction mixture stirred at room temperature for 2.5h. Upon completion the reaction mixture was acidified to ~pH 2-3 using 1N HCl and the solvents removed under vacuum to give (R)-4-((2-chloro-5-((2-fluoro-3-hydroxy-3-methylbutyl)carbamoyl)pyridin-4-yl)amino)bicyclo[2.2.2]octane-1-carboxylic acid which was used without further purification.

ES/MS: 428.4 (M+H<sup>+</sup>).

**(R)-4-((4-(1,3,4-thiadiazol-2-yl)bicyclo[2.2.2]octan-1-yl)amino)-6-chloro-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide:** Dissolved (R)-4-((2-chloro-5-((2-fluoro-3-hydroxy-3-methylbutyl)carbamoyl)pyridin-4-yl)amino)bicyclo[2.2.2]octane-1-carboxylic acid (100 mg, 0.23 mmol) in 5 mL of DMF, O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (118 mg, 0.28 mmol) stirred for 30 seconds then added diisopropylethylamine (0.06 mL, 0.35 mmol). Formic acid hydrazide (140.3 mg, 2.34 mmol) was added to the mixture after 30 minutes. The reaction was stirred for 16 hour. Poured into water and extracted with EtOAc. Concentrated residue has significant amount of white

25

solid, filtered washing with DCM which gave 50 mg of crude product. The crude product (50 mg, 0.11 mmol) and Lawesson's reagent (51.6 mg, 0.13 mmol) in 3 mL of dioxane, was heated for 2h at 80 degree. Cooled it down and diluted with 30 mL of EtOAc. The organic layer was washed with water and brine. The mixture was purified by flash column (eluent:

- 5 EtOAc/hexanes) to give (R)-4-(((4-(1,3,4-thiadiazol-2-yl)bicyclo[2.2.2]octan-1-yl)amino)-6-chloro-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide.

ES/MS: 468.2 (M+H<sup>+</sup>).

**(R)-4-(((4-(1,3,4-thiadiazol-2-yl)bicyclo[2.2.2]octan-1-yl)amino)-6-(3-**

**cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide**

- 10 **(Example 61):** (R)-4-(((4-(1,3,4-thiadiazol-2-yl)bicyclo[2.2.2]octan-1-yl)amino)-6-chloro-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide was converted to the final product (R)-4-(((4-(1,3,4-thiadiazol-2-yl)bicyclo[2.2.2]octan-1-yl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide **(Example 61)** in the manner described in step 2 of **Procedure 1** substituting 6-chloro-4-(((1r,4R)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide with (R)-4-(((4-
- 15 (1,3,4-thiadiazol-2-yl)bicyclo[2.2.2]octan-1-yl)amino)-6-chloro-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide.

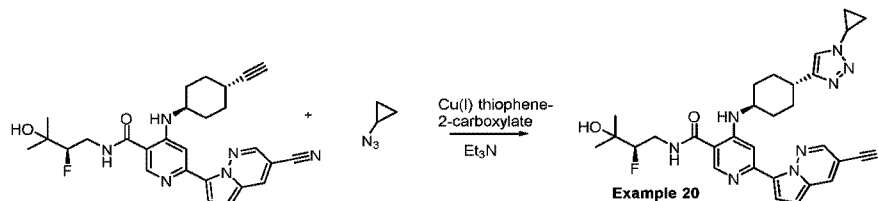
ES/MS: 575.31 (M+H<sup>+</sup>).

- 20 <sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) δ 9.38 (s, 1H), 8.80 - 8.73 (m, 2H), 8.56 (s, 1H), 8.39 (s, 1H), 7.95 (d, J = 5.1 Hz, 1H), 7.22 (d, J = 5.1 Hz, 1H), 4.58 - 4.27 (m, 1H), 3.92 (ddd, J = 36.6, 14.6, 2.1 Hz, 1H), 3.48 (td, J = 15.7, 9.4 Hz, 1H), 2.32 (s, 12H), 1.28 (d, J = 1.6 Hz, 6H).

### Procedure 10: Example 20

**6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-cyclopropyl-1H-1,2,3-triazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide**

- 25 **(Example 20)**



**6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-cyclopropyl-1H-1,2,3-triazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide**

**(Example 20):** 6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-

ethynylcyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (18 mg, 0.037 mmol) (obtained in the manner described in **Procedure 1** substituting (1r,4r)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexan-1-amine hydrochloride **I-24** with (1r,4r)-4-ethynylcyclohexan-1-amine hydrochloride) was dissolved in DMF (0.6 mL) after which

5 copper(I) thiophene-2-carboxylate (2 mg, 0.009 mmol), cyclopropyl azide (6 mg, 0.074 mmol) and triethylamine (15  $\mu$ L, 0.11 mmol) were added and the resulting mixture stirred for 1h at room temperature. Upon completion the crude mixture was filtered and purified by HPLC prep (eluent: water / MeCN \*0.1% TFA) to give 6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-cyclopropyl-1H-1,2,3-triazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-

10 methylbutyl)nicotinamide (**Example 20**).

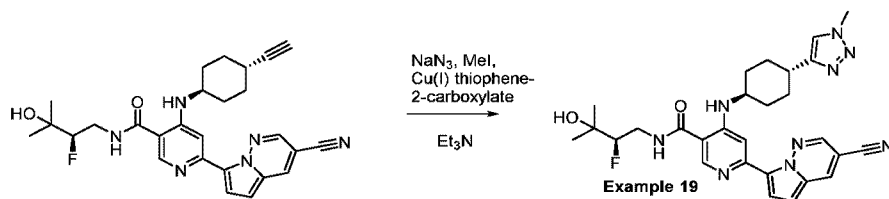
ES/MS: 572.3 (M+H<sup>+</sup>).

<sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>)  $\delta$  8.78 (d, J = 2.2 Hz, 1H), 8.71 (d, J = 2.2 Hz, 1H), 8.59 (s, 1H), 8.05 (d, J = 5.1 Hz, 1H), 7.97 (s, 1H), 7.85 (s, 1H), 7.24 (d, J = 5.1 Hz, 1H), 4.45 (dd, J = 49.1, 7.5 Hz, 1H), 4.07 - 3.78 (m, 2H), 3.61 - 3.42 (m, 1H), 2.93 - 2.79 (m, 1H), 2.26

15 (dd, J = 39.3, 12.9 Hz, 4H), 1.73 (dd, J = 56.0, 12.8 Hz, 4H), 1.37 - 1.27 (m, 6H), 1.27 - 1.14 (m, 4H).

**Procedure 11: Example 19:**

**6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(1-methyl-1H-1,2,3-triazol-4-yl)cyclohexyl)amino)nicotinamide**



**6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(1-methyl-1H-1,2,3-triazol-4-yl)cyclohexyl)amino)nicotinamide (Example 19):**

Sodium azide (16 mg, 0.25 mmol), methyl iodide (12  $\mu$ L, 0.18 mmol), and DMF (0.5 mL) were combined in a vial and stirred at 50  $^{\circ}$ C for 1h. 6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-ethynylcyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (15 mg, 0.031 mmol) (obtained in the manner described in **Procedure 1** substituting (1r,4r)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexan-1-amine hydrochloride **I-24** with (1r,4r)-4-ethynylcyclohexan-1-amine hydrochloride) and copper(I) thiophene-2-carboxylate (1 mg, 0.0077 mmol) were added and the resulting mixture stirred for 4h at 50  $^{\circ}$ C. Triethylamine (13

25

30  $\mu$ L, 0.092 mmol) was then added and the reaction mixture stirred for 1h at room temperature.

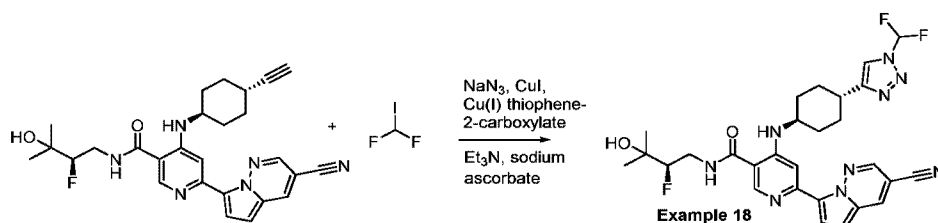
Upon completion the crude mixture was filtered and purified by HPLC prep (eluent: water / MeCN \*0.1% TFA) to give 6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(1-methyl-1H-1,2,3-triazol-4-yl)cyclohexyl)amino)nicotinamide (**Example 19**).

5 ES/MS: 546.3 (M+H<sup>+</sup>).

<sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) δ 8.77 (d, J = 2.2 Hz, 1H), 8.70 (d, J = 2.2 Hz, 1H), 8.59 (s, 1H), 8.04 (d, J = 5.0 Hz, 1H), 7.96 (s, 1H), 7.77 (s, 1H), 7.23 (d, J = 5.1 Hz, 1H), 4.45 (ddd, J = 49.2, 9.4, 2.1 Hz, 1H), 4.10 (s, 3H), 4.02 - 3.86 (m, 1H), 3.55 - 3.44 (m, 2H), 2.88 (d, J = 3.5 Hz, 1H), 2.26 (dd, J = 36.9, 12.9 Hz, 4H), 1.90 - 1.52 (m, 4H), 1.35 - 1.25 (m, 6H).

10 **Procedure 12: Example 18:**

**6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-(difluoromethyl)-1H-1,2,3-triazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide**



**6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-(difluoromethyl)-1H-1,2,3-triazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide**

15 **(Example 18):** Sodium azide (6 mg, 0.10 mmol), difluoromethyl iodide (10% in THF, 16 mg, 0.09 mmol), and DMF (0.5 mL) were combined in a vial and stirred at 50 °C for 1h. 6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-ethynylcyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (15 mg, 0.031 mmol) (obtained in the manner described in

20 **Procedure 1** substituting (1r,4r)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexan-1-amine hydrochloride **I-24** with (1r,4r)-4-ethynylcyclohexan-1-amine hydrochloride), copper(I) thiophene-2-carboxylate (2 mg, 0.0092 mmol), copper(I) iodide (3 mg, 0.015 mmol), sodium ascorbate (3 mg, 0.018 mmol) and triethylamine (26 μL, 0.18 mmol) was then added and the reaction mixture stirred for 1h at room temperature. Upon completion the crude mixture was

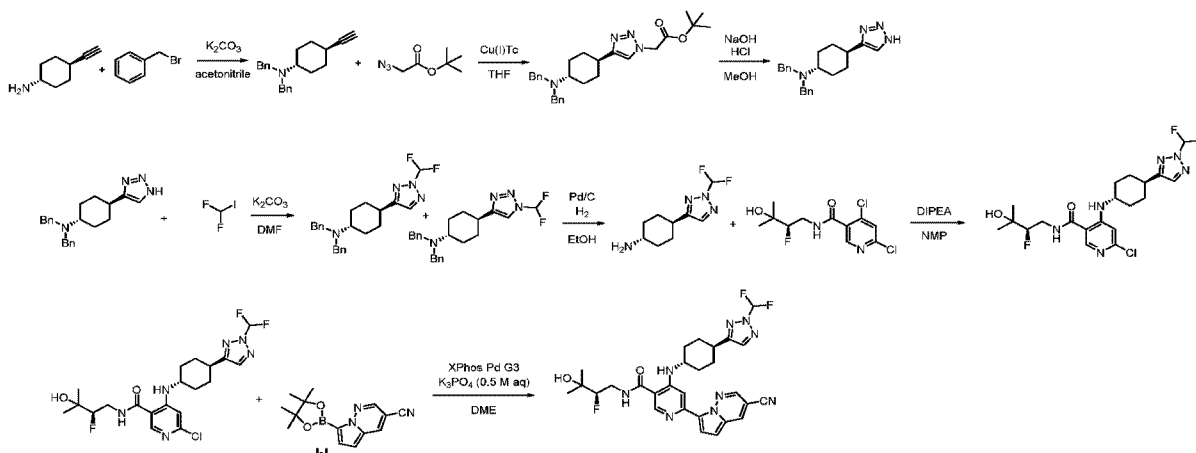
25 filtered and purified by HPLC prep (eluent: water / MeCN \*0.1% TFA) to give 6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-(difluoromethyl)-1H-1,2,3-triazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (**Example 18**).

ES/MS: 582.2 (M+H<sup>+</sup>).

<sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) δ 8.77 (d, J = 2.2 Hz, 1H), 8.71 (d, J = 2.2 Hz, 1H), 8.59 (s, 1H), 8.32 (s, 1H), 8.14 - 7.78 (m, 3H), 7.24 (d, J = 5.0 Hz, 1H), 4.45 (dd, J = 49.1, 8.4 Hz, 1H), 3.98 (dd, J = 23.8, 12.3 Hz, 1H), 3.57 - 3.44 (m, 2H), 3.04 - 2.91 (m, 1H), 2.36 - 2.24 (m, 4H), 1.76 (dd, J = 63.9, 12.5 Hz, 4H), 1.36 - 1.29 (m, 6H).

### 5 Procedure 13: Example 75:

#### 6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1*r*,4*R*)-4-(2-(difluoromethyl)-2H-1,2,3-triazol-4-yl)cyclohexyl)amino)-N-((*R*)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide



#### trans-N,N-dibenzyl-4-ethynylcyclohexan-1-amine: To trans-4-

- 10 ethynylcyclohexanamine (1 g, 8.12 mmol) in acetonitrile (40 mL) was added benzyl bromide (2 mL, 2.03 mmol) and potassium carbonate (4.49 g, 32.5 mmol). The mixture was heated at 60 °C for 48 hrs. Afterward, the mixture was allowed to cool to rt and water (100 mL) was added. The mixture was diluted with EtOAc (150 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were dried over MgSO<sub>4</sub>,  
 15 filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (eluent: EtOAc/hexanes).

ES/MS: 304.362 (M+H<sup>+</sup>)

- <sup>1</sup>H NMR (400 MHz, Chloroform-d) δ 7.40 – 7.35 (m, 4H), 7.34 – 7.29 (m, 2H), 7.26 – 7.17 (m, 2H), 3.63 (s, 4H), 2.52 (tt, J = 12.8, 4.7 Hz, 1H), 2.16 (td, J = 12.2, 11.8, 2.7 Hz, 1H),  
 20 2.10 – 1.86 (m, 5H), 1.46 – 1.21 (m, 4H).

**trans-tert-butyl 2-[4-[4-(dibenzylamino)cyclohexyl]triazol-1-yl]acetate:** To a solution of trans-N,N-dibenzyl-4-ethynylcyclohexan-1-amine (1.69 g, 5.57 mmol) in THF (50 mL), was added copper(I) thiophene-2-carboxylate (319 mg, 1.67 mmol), followed by tert-butyl 2-azidoacetate (1.31 g, 8.35 mmol) and stirred at rt in ambient atmosphere for 30 minutes. Upon

completion, the mixture was poured into sat. aq. NaHCO<sub>3</sub> (50 mL), and extracted with EtOAc (3x75 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude residue was carried forward without further purification.

ES/MS: 461.431 (M+H<sup>+</sup>)

5        **trans-N,N-dibenzyl-4-(1H-triazol-4-yl)cyclohexanamine:** To a RBF with trans-tert-butyl 2-[4-[4-(dibenzylamino)cyclohexyl]triazol-1-yl]acetate (2.57 g, 5.57 mmol) was added MeOH (30 mL), followed by NaOH (1M aq, 12.3 mL, 12.3 mmol). The mixture was stirred at rt for 30 minutes. To the mixture was slowly added HCl (1M aq, 12.3 mL, 12.3 mmol), and the mixture was poured into water (30 mL) and EtOAc (100 mL). The layers were separated, and  
10 the aqueous layer was extracted with EtOAc (2x 50 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (eluent: EtOAc/hexanes, then MeOH/EtOAc) to afford the product.

ES/MS: 347.299 (M+H<sup>+</sup>)

15        <sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) δ 7.43 – 7.35 (m, 4H), 7.33 – 7.25 (m, 4H), 7.25 – 7.14 (m, 2H), 3.67 (s, 4H), 2.72 (ddt, J = 12.3, 7.2, 3.6 Hz, 1H), 2.68 – 2.47 (m, 1H), 2.19 – 1.94 (m, 4H), 1.62 (qd, J = 12.6, 3.2 Hz, 2H), 1.38 (qd, J = 12.8, 3.1 Hz, 2H).

20        **trans-N,N-dibenzyl-4-[2-(difluoromethyl)triazol-4-yl]cyclohexanamine:** To a 100 mL RBF was added trans-N,N-dibenzyl-4-(1H-triazol-4-yl)cyclohexanamine (900 mg, 2.6 mmol), followed by potassium carbonate (718 mg, 5.2 mmol), and DMF (10 mL). Difluoro(iodo)methane (10% wt solution in THF, 5.55 g, 3.12 mmol) was added, and the mixture was stirred at rt overnight. The mixture was partitioned between EtOAc (150 mL) and water (50 mL), and the layers separated. The organic layer was washed with water (2x 50 mL), and the organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure.  
25 The crude material was purified by silica gel chromatography (eluent: EtOAc/hexanes, then MeOH/EtOAc) to afford the product as an approximately 10:1 mixture of triazole regioisomers (terminal:internal), which were carried through until the end of the synthetic sequence.

ES/MS: 397.514 (M+H<sup>+</sup>)

30        **trans-4-(2-(difluoromethyl)-2H-1,2,3-triazol-4-yl)cyclohexan-1-amine:** To 100 mL RBF was added trans-N,N-dibenzyl-4-[2-(difluoromethyl)triazol-4-yl]cyclohexanamine (10:1 mixture of terminal:internal triazole isomers) (600 mg, 1.51 mmol), and the material was dissolved in ethanol (10 mL). Palladium on carbon (10% wt, 81 mg) was added, and the reaction

was degassed with H<sub>2</sub>, then stirred at 35°C for 72 hours under a hydrogen atmosphere (balloon). The crude mixture was degassed with argon for 1 minute, then the solids were removed by filtration through celite. The crude mixture was concentrated under reduced pressure, and used directly for the next step.

- 5           **6-chloro-4-((trans-4-(2-(difluoromethyl)-2H-1,2,3-triazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide:** To a microwave vial was added trans-4-(2-(difluoromethyl)-2H-1,2,3-triazol-4-yl)cyclohexan-1-amine (209 mg, 0.966 mmol), 4,6-dichloro-N-[(2R)-2-fluoro-3-hydroxy-3-methyl-butyl]pyridine-3-carboxamide (190 mg, 0.644 mmol) (prepared in an identical fashion to Example 42, step 1), and NMP (2 mL).
- 10   N,N-Diisopropylethylamine (0.28 mL, 1.61 mL) was added, and the vial was sealed and heated at 150 °C in a microwave reactor for 1 hour. The crude mixture was dissolved in EtOAc (50 mL), then washed once with water (20 mL), and once with brine (20 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (eluent: EtOAc/hexanes, then MeOH/EtOAc).

15           ES/MS: 475.605 (M+H<sup>+</sup>)

- 6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-[[4-[2-(difluoromethyl)triazol-4-yl]cyclohexyl]amino]-N-[(2R)-2-fluoro-3-hydroxy-3-methyl-butyl]pyridine-3-carboxamide (75):** 6-chloro-4-((trans-4-(2-(difluoromethyl)-2H-1,2,3-triazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide (10:1 terminal:internal mixture of triazole
- 20   isomers) (0.1 g, 0.211 mmol) and 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[1,2-b]pyridazine-3-carbonitrile **I-1** (0.80 g, 0.295 mmol) were added to a microwave vial followed by DME (1.0 mL), XPhos Pd G3 (23.8 mg, 0.0316 mmol) and K<sub>3</sub>PO<sub>4</sub> (0.5M in water, 0.842 mL, 0.421 mmol). The resulting mixture was purged with argon for 30 seconds, sealed and heated to
- 25   RP-HPLC (eluent: water / MeCN \*0.1% TFA) to afford the product as a 10:1 mixture of terminal:internal triazole isomers. The desired internal triazole isomer was separated by SFC (IC column, 50% EtOH-NH<sub>3</sub>). The separated material was re-subjected to RP-HPLC (eluent: water / MeCN \*0.1% TFA) to afford **(75)** as a TFA salt.

          ES/MS: 582.286 (M+H<sup>+</sup>)

- 30           <sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) δ 8.79 (d, J = 2.2 Hz, 1H), 8.72 (d, J = 2.2 Hz, 1H), 8.61 (s, 1H), 8.23 – 7.89 (m, 3H), 7.82 (s, 1H), 7.25 (d, J = 5.1 Hz, 1H), 4.60 – 4.32 (m, 1H),

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4.10–3.71 (m, 2H), 3.63–3.43 (m, 1H), 3.24–3.08 (m, 1H), 2.29 (dd, J = 47.0, 12.9 Hz, 4H), 1.92–1.60 (m, 4H), 1.36–1.25 (m, 6H).

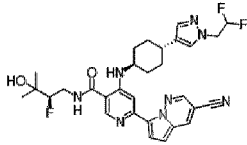
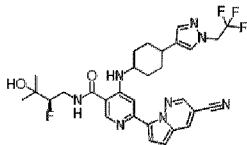
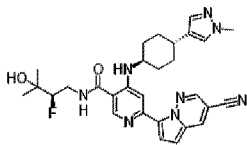
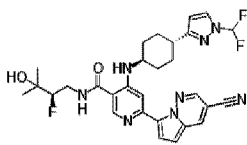
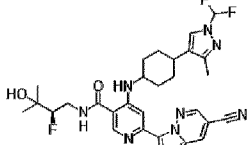
<sup>19</sup>F NMR (376 MHz, Methanol-d<sub>4</sub>) δ -98.98 (d, J = 57.3 Hz), -194.37 – -197.80 (m).

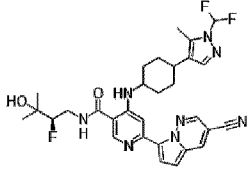
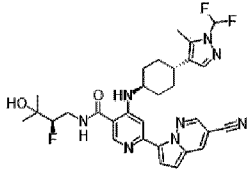
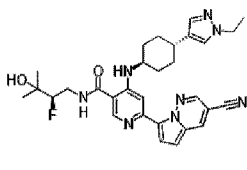
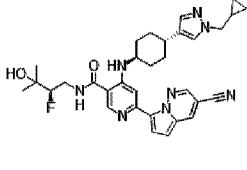
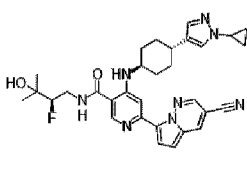
## COMPOUND TABLE

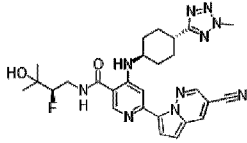
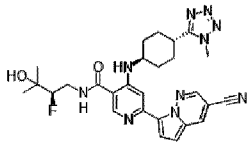
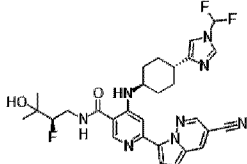
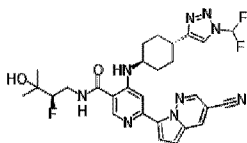
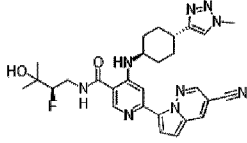
The compounds in **Table 1** were prepared according to the Examples and Procedures described herein using the appropriate starting materials and protecting group chemistry as needed.

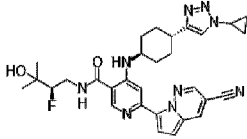
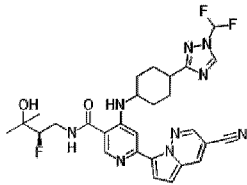
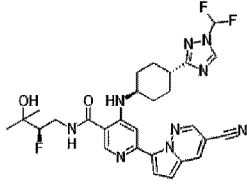
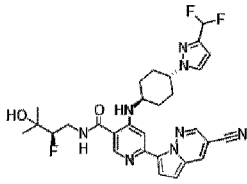
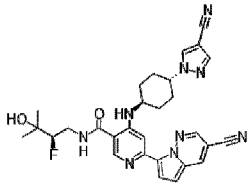
**Table 1**

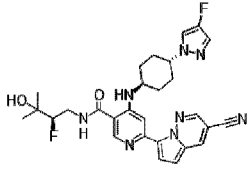
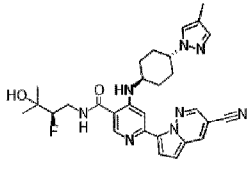
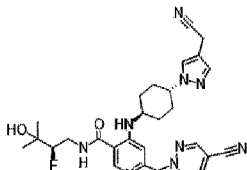
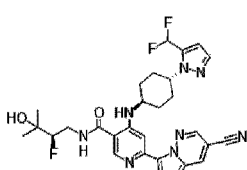
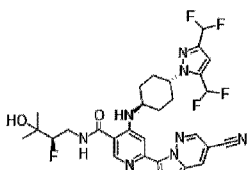
Structure	#	ES/MS m/z	Name	Procedure
	1	531.3	4-(((1r,4R)-4-(1H-pyrazol-4-yl)cyclohexyl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	6
	2	531.3	4-(((1s,4S)-4-(1H-pyrazol-4-yl)cyclohexyl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	6
	3	581.2	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-(difluoromethyl)-1H-pyrazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	2
	4	599.6	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(1-(trifluoromethyl)-1H-pyrazol-4-yl)cyclohexyl)amino)nicotinamide	2

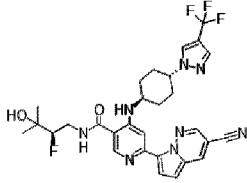
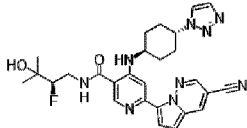
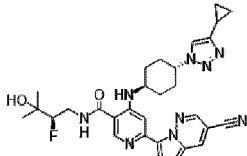
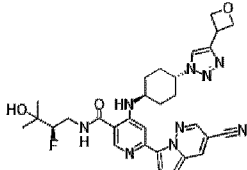
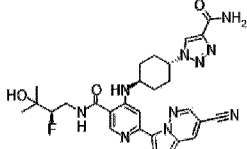
Structure	#	ES/MS m/z	Name	Procedure
	5	595.3	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	2
	6	613.3	(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-(2-fluoro-3-hydroxy-3-methylbutyl)-4-((4-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)cyclohexyl)amino)nicotinamide	1
	7	545.3	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(1-methyl-1H-pyrazol-4-yl)cyclohexyl)amino)nicotinamide	4
	8	581.4	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-(difluoromethyl)-1H-pyrazol-3-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	3
	9	595.35	(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-((4-(1-(difluoromethyl)-3-methyl-1H-pyrazol-4-yl)cyclohexyl)amino)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1

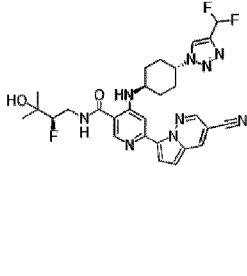
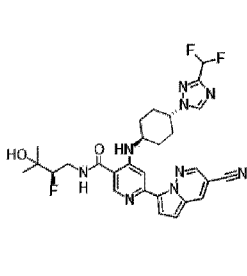
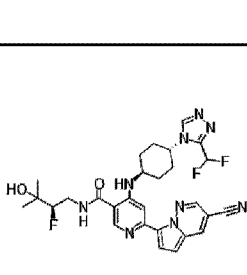
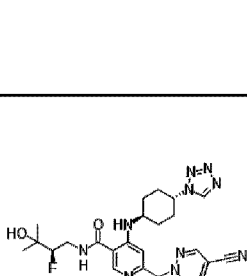
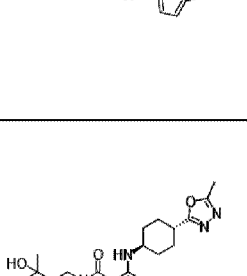
Structure	#	ES/MS m/z	Name	Procedure
	10	595.38	(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-((1-(difluoromethyl)-5-methyl-1H-pyrazol-4-yl)cyclohexyl)amino)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1
	11	595.34	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-(difluoromethyl)-5-methyl-1H-pyrazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	2
	12	559.5	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-ethyl-1H-pyrazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	4
	13	585.4	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	4
	14	571.3	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-cyclopropyl-1H-pyrazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	4

Structure	#	ES/MS m/z	Name	Procedure
	15	547.3	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(2-methyl-2H-tetrazol-5-yl)cyclohexyl)amino)nicotinamide	1
	16	547.2	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(1-methyl-1H-tetrazol-5-yl)cyclohexyl)amino)nicotinamide	1
	17	581.4	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-(difluoromethyl)-1H-imidazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	2
	18	582.193	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-(difluoromethyl)-1H-1,2,3-triazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	12
	19	546.325	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(1-methyl-1H-1,2,3-triazol-4-yl)cyclohexyl)amino)nicotinamide	11

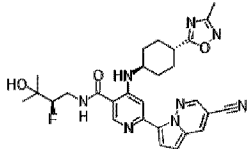
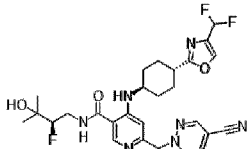
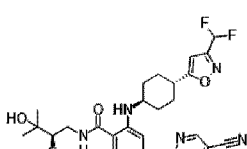
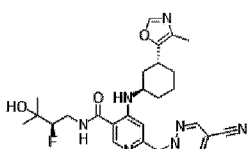
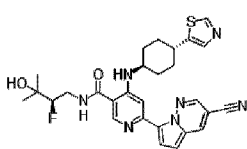
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	20	572.290	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-cyclopropyl-1H-1,2,3-triazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	10
	21	582.34	(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((4-(1-(difluoromethyl)-1H-1,2,4-triazol-3-yl)cyclohexyl)amino)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1
	22	582.56	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(1-(difluoromethyl)-1H-1,2,4-triazol-3-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	2
	23	581.6	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(3-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	5
	24	556.38	4-(((1r,4R)-4-(4-cyano-1H-pyrazol-1-yl)cyclohexyl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	5

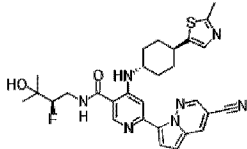
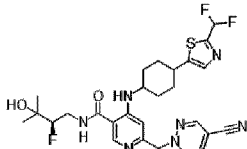
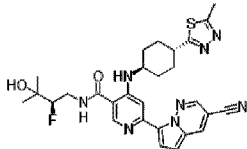
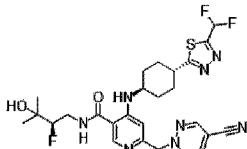
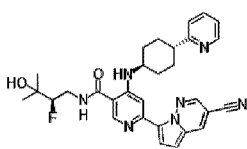
Structure	#	ES/MS m/z	Name	Procedure
	25	549.27	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(4-fluoro-1H-pyrazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	5
	26	545.6	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(4-methyl-1H-pyrazol-1-yl)cyclohexyl)amino)nicotinamide	5
	27	570.3	4-(((1r,4R)-4-(4-(cyanomethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	5
	28	581.3	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(5-(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	5
	29	631.33	4-(((1r,4R)-4-(3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	5

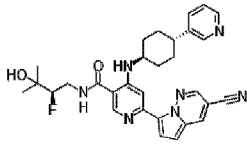
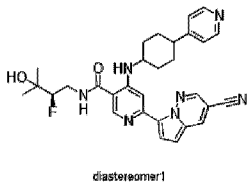
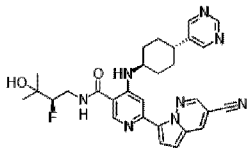
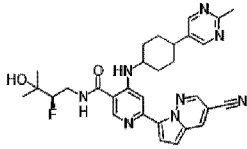
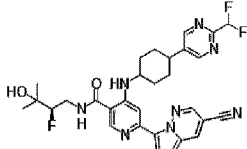
Structure	#	ES/MS m/z	Name	Procedure
	30	599.33	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(4-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)amino)nicotinamide	5
	31	532.27	4-(((1r,4R)-4-(1H-1,2,3-triazol-1-yl)cyclohexyl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1
	32	572.23	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1
	33	588.30	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(4-(oxetan-3-yl)-1H-1,2,3-triazol-1-yl)cyclohexyl)amino)nicotinamide	1
	34	575.20	4-(((1r,4R)-4-(4-carbamoyl-1H-1,2,3-triazol-1-yl)cyclohexyl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1

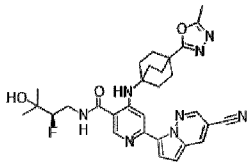
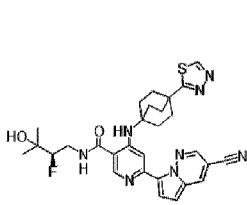
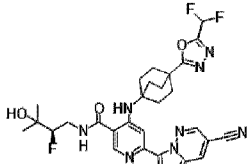
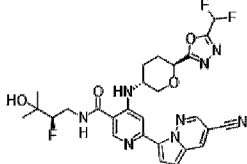
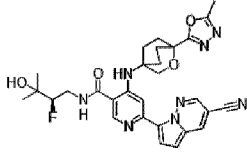
Structure	#	ES/MS m/z	Name	Procedure
	35	582.38	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(4-(difluoromethyl)-1H-1,2,3-triazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1
	36	582.31	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(3-(difluoromethyl)-1H-1,2,4-triazol-1-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	5
	37	582.27	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(3-(difluoromethyl)-4H-1,2,4-triazol-4-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	5
	38	533.1	4-(((1r,4R)-4-(1H-tetrazol-1-yl)cyclohexyl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1
	39	547.3	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(5-methyl-1,3,4-oxadiazol-2-yl)cyclohexyl)amino)nicotinamide	1

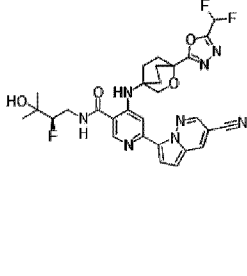
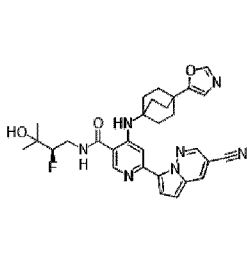
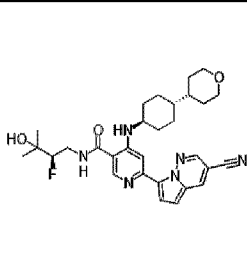
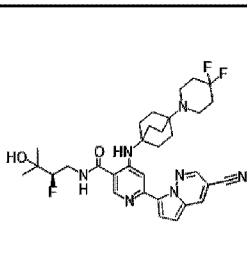
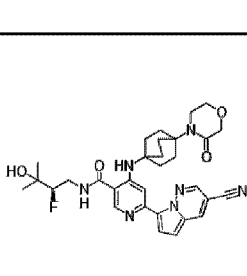
Structure	#	ES/MS m/z	Name	Procedure
	40	577.319	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)cyclohexyl)amino)nicotinamide	1
	41	573.5	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1
	42	583.4	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1
	43	601.3	(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-((4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-4-fluorocyclohexyl)amino)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1
	44	547.3	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(5-methyl-1,2,4-oxadiazol-3-yl)cyclohexyl)amino)nicotinamide	1

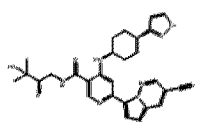
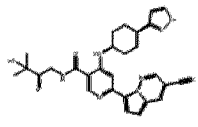
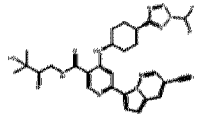
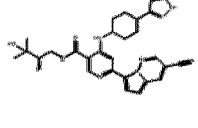
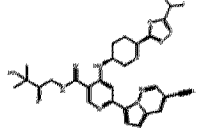
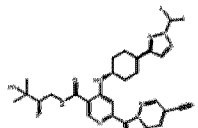
Structure	#	ES/MS m/z	Name	Procedure
	45	547.3	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(3-methyl-1,2,4-oxadiazol-5-yl)cyclohexyl)amino)nicotinamide	1
	46	582.43	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(4-(difluoromethyl)oxazol-2-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	2
	47	582.4	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(3-(difluoromethyl)isoxazol-5-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1
	48	546.283	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1R,3R)-3-(4-methyloxazol-5-yl)cyclohexyl)amino)nicotinamide	1
	49	548.241	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(thiazol-5-yl)cyclohexyl)amino)nicotinamide	2

Structure	#	ES/MS m/z	Name	Procedure
	50	562.195	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(2-methylthiazol-5-yl)cyclohexyl)amino)nicotinamide	2
	51	599.022	(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((4-(2-(difluoromethyl)thiazol-5-yl)cyclohexyl)amino)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1
	52	563.3	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(5-methyl-1,3,4-thiadiazol-2-yl)cyclohexyl)amino)nicotinamide	1
	53	599.3	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1
	54	542.24	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(pyridin-2-yl)cyclohexyl)amino)nicotinamide	2

Structure	#	ES/MS m/z	Name	Procedure
	55	542.267	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(pyridin-3-yl)cyclohexyl)amino)nicotinamide	2
 diastereomer1	56	542.268	(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-(2-fluoro-3-hydroxy-3-methylbutyl)-4-((4-(pyridin-4-yl)cyclohexyl)amino)nicotinamide	2
	57	543.275	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(pyrimidin-5-yl)cyclohexyl)amino)nicotinamide	2
	58	557.27	(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-(2-fluoro-3-hydroxy-3-methylbutyl)-4-((4-(2-methylpyrimidin-5-yl)cyclohexyl)amino)nicotinamide	1
	59	593.329	(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-((4-(2-(difluoromethyl)pyrimidin-5-yl)cyclohexyl)amino)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1

Structure	#	ES/MS m/z	Name	Procedure
	60	573.4	(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-(2-fluoro-3-hydroxy-3-methylbutyl)-4-((4-(5-methyl-1,3,4-oxadiazol-2-yl)bicyclo[2.2.2]octan-1-yl)amino)nicotinamide	1
	61	575.31	(R)-4-((4-(1,3,4-thiadiazol-2-yl)bicyclo[2.2.2]octan-1-yl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	9
	62	609.57	(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-((4-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)bicyclo[2.2.2]octan-1-yl)amino)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1
	63	585.5	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((3R,6S)-6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)tetrahydro-2H-pyran-3-yl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1
	64	575.4	(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-(2-fluoro-3-hydroxy-3-methylbutyl)-4-((1-(5-methyl-1,3,4-oxadiazol-2-yl)-2-oxabicyclo[2.2.2]octan-4-yl)amino)nicotinamide	1

Structure	#	ES/MS m/z	Name	Procedure
	65	611.3	(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-((1-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-2-oxabicyclo[2.2.2]octan-4-yl)amino)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1
	66	558.349	(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-(2-fluoro-3-hydroxy-3-methylbutyl)-4-((4-(oxazol-5-yl)bicyclo[2.2.2]octan-1-yl)amino)nicotinamide	1
	67	549.5	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)-4-(((1r,4R)-4-(tetrahydro-2H-pyran-4-yl)cyclohexyl)amino)nicotinamide	2
	68	610.4	(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-((4-(4,4-difluoropiperidin-1-yl)bicyclo[2.2.2]octan-1-yl)amino)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	7
	69	590.65	(R)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-(2-fluoro-3-hydroxy-3-methylbutyl)-4-((4-(3-oxomorpholino)bicyclo[2.2.2]octan-1-yl)amino)nicotinamide	8

Structure	#	ES/MS m/z	Name	Procedure
	70	531.6	4-(((1r,4R)-4-(1H-pyrazol-3-yl)cyclohexyl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	2
	71	531.6	4-(((1s,4S)-4-(1H-pyrazol-3-yl)cyclohexyl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	2
	72	583.2	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(2-(difluoromethyl)-2H-tetrazol-5-yl)cyclohexyl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1
	73	531.4	(R)-4-((4-(1H-pyrazol-3-yl)cyclohexyl)amino)-6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-(2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1
	74	585.6	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((3S,6R)-6-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)tetrahydro-2H-pyran-3-yl)amino)-N-((R)-2-fluoro-3-hydroxy-3-methylbutyl)nicotinamide	1
	75	582.29	6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-4-(((1r,4R)-4-(2-(difluoromethyl)-2H-1,2,3-triazol-4-yl)cyclohexyl)amino)-N-((R)-2-	1

Structure	#	ES/MS m/z	Name	Procedure
			fluoro-3-hydroxy-3-methylbutyl)nicotinamide	

**<sup>1</sup>H NMR**

Proton NMR data is shown in Table 2.

**Table 2**

Compound	<sup>1</sup> H-NMR
1	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.77 (d, J = 2.1 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.60 (s, 1H), 8.05 (d, J = 5.1 Hz, 1H), 7.93 (s, 1H), 7.57 (s, 2H), 7.23 (d, J = 5.0 Hz, 1H), 4.45 (ddd, J = 49.1, 9.4, 2.1 Hz, 1H), 4.10 - 3.85 (m, 2H), 3.52 (ddd, J = 16.0, 14.5, 9.4 Hz, 1H), 2.71 (t, J = 11.5 Hz, 1H), 2.38 - 2.23 (m, 2H), 2.24 - 2.05 (m, 2H), 1.89 - 1.52 (m, 4H), 1.32 (d, J = 1.7 Hz, 6H), 0.97 - 0.78 (m, 1H).
2	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.78 (d, J = 2.2 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.63 (s, 1H), 8.03 (d, J = 5.1 Hz, 1H), 7.90 (s, 1H), 7.56 (s, 2H), 7.24 (d, J = 5.0 Hz, 1H), 4.45 (ddd, J = 49.1, 9.4, 2.2 Hz, 1H), 4.26 (s, 1H), 3.96 (ddd, J = 36.5, 14.5, 2.2 Hz, 1H), 3.56 - 3.42 (m, 1H), 2.82 (t, J = 10.5 Hz, 1H), 2.03 (d, J = 11.0 Hz, 7H), 1.77 (d, J = 11.4 Hz, 2H), 1.31 (d, J = 1.7 Hz, 6H), 0.97 - 0.82 (m, 1H).
3	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.61 - 8.57 (m, 2H), 8.55 (d, J = 2.2 Hz, 1H), 8.24 (s, 1H), 7.96 (s, 1H), 7.83 (d, J = 4.8 Hz, 1H), 7.72 (s, 1H), 7.43 (t, J = 59.9 Hz, 1H), 7.11 (d, J = 4.9 Hz, 1H),

Compound	1H-NMR
	4.45 (ddd, J = 49.0, 9.1, 2.2 Hz, 1H), 3.90 (ddd, J = 35.6, 14.5, 2.3 Hz, 1H), 3.70 - 3.58 (m, 1H), 3.57 - 3.41 (m, 1H), 2.70 (t, J = 11.8 Hz, 1H), 2.36 (d, J = 12.4 Hz, 2H), 2.18 (d, J = 13.2 Hz, 2H), 1.69 (q, J = 11.5 Hz, 2H), 1.61 - 1.44 (m, 2H), 1.32 (d, J = 1.7 Hz, 6H).
4	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.78 – 8.72 (m, 1H), 8.68 (d, J = 1.7 Hz, 1H), 8.57 (s, 1H), 8.09 – 7.96 (m, 2H), 7.91 (s, 1H), 7.81 (s, 1H), 7.21 (dd, J = 5.1, 1.6 Hz, 1H), 4.54 – 4.31 (m, 1H), 4.07 – 3.83 (m, 2H), 3.59 – 3.42 (m, 1H), 2.80 – 2.65 (m, 2H), 2.32 – 2.24 (m, 2H), 2.22 – 2.12 (m, 2H), 1.81 – 1.54 (m, 4H), 1.29 (d, J = 1.7 Hz, 6H).
5	1H NMR (400 MHz, Methanol-d4) $\delta$ 9.04 (t, J = 5.5 Hz, 0H), 8.77 (d, J = 2.2 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.60 (s, 1H), 8.05 (d, J = 5.1 Hz, 1H), 7.93 (s, 1H), 7.59 (s, 1H), 7.51 (s, 1H), 7.23 (d, J = 5.1 Hz, 1H), 6.39 - 5.97 (m, 1H), 4.62 - 4.33 (m, 4H), 4.05 - 3.83 (m, 3H), 3.52 (ddd, J = 16.1, 14.4, 9.4 Hz, 1H), 2.78 - 2.61 (m, 2H), 2.29 (d, J = 11.5 Hz, 3H), 2.16 (d, J = 12.4 Hz, 3H), 1.82 - 1.56 (m, 6H), 1.32 (d, J = 1.7 Hz, 6H).
6	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.60 (s, 1H), 8.58 (s, 1H), 8.57 - 8.55 (m, 2H), 8.50 (t, J = 2.9 Hz, 2H), 8.20 (s, 1H), 8.17 (s, 1H), 7.81 (dd, J = 4.8, 1.2 Hz, 2H), 7.66 (d, J = 2.0 Hz, 2H), 7.56 (d, J = 5.3 Hz, 2H), 7.09 (d, J = 4.9 Hz, 2H), 4.45 (ddd, J = 48.9, 9.2, 2.3 Hz, 2H), 3.90 (ddd, J = 35.4, 14.7, 2.5 Hz, 3H), 3.58 - 3.41 (m, 1H), 2.76 (s, 1H), 2.66 (t, J = 11.9 Hz, 1H), 2.34 (d, J = 12.0 Hz, 2H), 2.16 (d, J = 13.1 Hz, 2H), 1.98 (d, J = 43.0 Hz, 7H), 1.85 - 1.57 (m, 3H), 1.50 (q, J = 11.3 Hz, 2H), 1.31 (dd, J = 3.2, 1.6 Hz, 12H).
7	1H NMR (400 MHz, Methanol-d4) $\delta$ 9.01 (d, J = 5.9 Hz, 0H), 8.77 (d, J = 2.2 Hz, 1H), 8.69 (d, J = 2.1 Hz, 1H), 8.59 (s, 1H), 8.04 (d, J = 5.1 Hz, 1H), 7.92 (s, 1H), 7.48 (s, 1H), 7.41 (s, 1H), 7.23 (d, J = 5.1 Hz, 1H), 4.45 (ddd, J = 49.0, 9.4, 2.2 Hz, 1H), 4.12 – 3.88 (m, 1H), 3.87 (s, 3H), 3.69 – 3.41 (m, 1H), 2.72 – 2.53 (m, 0H), 2.28 (d, J = 10.9 Hz, 2H), 2.15 (d, J = 11.9 Hz, 2H), 1.65 (h, J = 12.0 Hz, 4H), 1.31 (d, J = 1.7 Hz, 6H).

Compound	<sup>1</sup> H-NMR
8	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.60 (s, 1H), 8.58 (d, J = 2.3 Hz, 1H), 8.54 (d, J = 2.2 Hz, 1H), 8.25 (s, 1H), 7.96 (d, J = 2.6 Hz, 1H), 7.83 (d, J = 4.9 Hz, 1H), 7.42 (t, J = 59.9 Hz, 1H), 7.11 (d, J = 4.9 Hz, 1H), 6.48 (d, J = 2.7 Hz, 1H), 4.57 – 4.30 (m, 0H), 3.91 (d, J = 52.2 Hz, 0H), 3.37 (s, 3H), 2.83 (s, 1H), 2.37 (d, J = 12.3 Hz, 2H), 2.19 (d, J = 13.4 Hz, 2H), 1.79 (d, J = 13.4 Hz, 1H), 1.53 (d, J = 12.2 Hz, 1H), 1.32 (d, J = 1.7 Hz, 6H).
9	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.75 (d, J = 2.1 Hz, 1H), 8.67 (dd, J = 6.3, 2.2 Hz, 1H), 8.59 (d, J = 19.3 Hz, 1H), 8.01 (t, J = 5.7 Hz, 1H), 7.84 (d, J = 25.6 Hz, 2H), 7.50 – 7.06 (m, 2H), 4.62 – 4.32 (m, 1H), 4.29 (s, 1H), 3.95 (dd, J = 36.3, 14.6 Hz, 1H), 3.68 – 3.36 (m, 1H), 2.70 (t, J = 11.5 Hz, 1H), 2.28 (d, J = 3.1 Hz, 3H), 2.08 (d, J = 12.9 Hz, 2H), 2.02 – 1.85 (m, 4H), 1.67 (q, J = 10.9, 9.7 Hz, 2H), 1.29 (d, J = 1.7 Hz, 6H).
10	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.84 – 8.52 (m, 3H), 8.01 (dd, J = 11.0, 5.1 Hz, 1H), 7.92 – 7.81 (m, 1H), 7.58 (d, J = 2.1 Hz, 1H), 7.41 (td, J = 58.6, 1.6 Hz, 1H), 7.21 (dd, J = 5.1, 1.8 Hz, 1H), 4.58 – 4.35 (m, 1H), 4.30 (s, 1H), 3.95 (dt, J = 36.6, 14.7 Hz, 1H), 3.54 (ddd, J = 24.6, 16.6, 9.8 Hz, 1H), 2.79 – 2.62 (m, 1H), 2.42 (d, J = 2.7 Hz, 3H), 2.28 (d, J = 11.8 Hz, 1H), 2.06 (t, J = 15.6 Hz, 1H), 1.97 (t, J = 14.2 Hz, 2H), 1.89 – 1.59 (m, 4H), 1.30 (dd, J = 4.7, 1.8 Hz, 6H).
11	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.59 (s, 1H), 8.47 (dd, J = 10.7, 2.3 Hz, 2H), 7.98 (s, 1H), 7.84 (d, J = 4.8 Hz, 1H), 7.61 – 7.56 (m, 1H), 7.41 – 7.05 (m, 2H), 4.42 (ddd, J = 48.7, 9.0, 2.5 Hz, 1H), 4.17 – 4.03 (m, 1H), 3.91 (ddd, J = 35.1, 14.6, 2.5 Hz, 1H), 3.64 – 3.43 (m, 1H), 2.61 (dt, J = 10.9, 7.1 Hz, 1H), 2.40 (s, 3H), 2.09 (d, J = 13.6 Hz, 2H), 1.98 – 1.63 (m, 6H), 1.29 (s, 6H).; <sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.53 (s, 1H), 8.43 (dd, J = 13.9, 2.3 Hz, 2H), 8.08 (s, 1H), 7.79 (d, J = 4.7 Hz, 1H), 7.53 (s, 1H), 7.28 (t, J = 58.8 Hz, 1H), 7.05 (d, J = 4.8 Hz, 1H), 4.53 – 4.28 (m, 1H), 3.98 – 3.79 (m, 1H), 3.60 (t, J = 11.5 Hz, 1H), 3.47 (td, J = 15.4, 8.9 Hz, 1H), 2.56 (t, J = 11.8 Hz, 1H), 2.40 (s, 3H), 2.33 (d, J = 12.6 Hz, 2H),

Compound	<sup>1</sup> H-NMR
	1.99 (d, J = 16.4 Hz, 3H), 1.78 – 1.38 (m, 3H), 1.28 (s, 6H).
12	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.77 (d, J = 2.2 Hz, 1H), 8.69 (d, J = 2.1 Hz, 1H), 8.61 (s, 1H), 8.05 (d, J = 5.0 Hz, 1H), 7.94 (s, 1H), 7.55 (s, 1H), 7.44 (d, J = 0.8 Hz, 1H), 7.24 (d, J = 5.1 Hz, 1H), 4.46 (ddd, J = 49.0, 9.3, 2.1 Hz, 1H), 4.18 (q, J = 7.3 Hz, 2H), 4.07 – 3.85 (m, 2H), 3.53 (ddd, J = 16.1, 14.5, 9.4 Hz, 1H), 3.08 (s, 1H), 2.94 (s, 1H), 2.74 – 2.57 (m, 1H), 2.40 – 2.23 (m, 2H), 2.22 – 2.01 (m, 4H), 1.76 – 1.55 (m, 4H), 1.46 (t, J = 7.3 Hz, 3H), 1.32 (d, J = 1.7 Hz, 6H).
13	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 9.03 (t, J = 5.6 Hz, 0H), 8.77 (d, J = 2.2 Hz, 1H), 8.69 (d, J = 2.1 Hz, 1H), 8.04 (d, J = 5.1 Hz, 1H), 7.92 (s, 1H), 7.59 (s, 1H), 7.44 (d, J = 0.8 Hz, 1H), 7.23 (d, J = 5.1 Hz, 1H), 4.45 (ddd, J = 49.1, 9.3, 2.1 Hz, 1H), 3.98 (d, J = 7.1 Hz, 2H), 3.91 (dd, J = 14.2, 2.6 Hz, 1H), 3.58 – 3.39 (m, 1H), 2.67 (td, J = 11.3, 3.5 Hz, 1H), 2.35 – 2.09 (m, 4H), 1.67 (ddt, J = 21.0, 13.2, 7.4 Hz, 4H), 1.45 – 1.20 (m, 6H), 0.68 – 0.51 (m, 2H), 0.40 (dt, J = 6.2, 4.6 Hz, 2H).
14	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.77 (d, J = 2.1 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.60 (s, 1H), 8.04 (d, J = 5.0 Hz, 1H), 7.93 (s, 1H), 7.58 (s, 1H), 7.43 (d, J = 0.8 Hz, 1H), 7.23 (d, J = 5.1 Hz, 1H), 4.45 (ddd, J = 49.1, 9.4, 2.1 Hz, 1H), 4.05 – 3.78 (m, 1H), 3.71 – 3.41 (m, 2H), 2.64 (td, J = 11.5, 3.9 Hz, 1H), 2.31 – 2.20 (m, 2H), 2.14 (d, J = 11.5 Hz, 2H), 1.80 – 1.55 (m, 4H), 1.31 (d, J = 1.7 Hz, 7H), 1.06 (ddt, J = 8.8, 4.3, 2.4 Hz, 4H).
15	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 8.83 (d, J = 2.3 Hz, 1H), 8.74 (d, J = 2.2 Hz, 1H), 8.73 (d, J = 2.7 Hz, 2H), 8.61 (d, J = 7.3 Hz, 1H), 8.16 (s, 1H), 7.84 (d, J = 4.8 Hz, 1H), 7.11 (d, J = 4.8 Hz, 1H), 4.85 (s, 1H), 4.38 (ddd, J = 49.2, 9.2, 2.1 Hz, 1H), 4.34 (s, 3H), 3.83 – 3.59 (m, 1H), 3.59 – 3.43 (m, 0H), 3.47 – 3.34 (m, 1H), 3.03 (tt, J = 11.8, 3.6 Hz, 1H), 2.20

Compound	<sup>1</sup> H-NMR
	(dd, J = 26.1, 12.9 Hz, 4H), 1.91 – 1.68 (m, 2H), 1.49 (q, J = 11.4 Hz, 2H), 1.18 (dd, J = 5.6, 1.6 Hz, 6H).
16	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ 8.84 (d, J = 2.2 Hz, 1H), 8.76 (d, J = 2.3 Hz, 1H), 8.73 (d, J = 3.1 Hz, 1H), 8.60 (d, J = 7.2 Hz, 1H), 8.17 (s, 1H), 7.84 (d, J = 4.8 Hz, 1H), 7.11 (d, J = 4.8 Hz, 1H), 4.85 (s, 1H), 4.38 (ddd, J = 49.3, 9.3, 2.2 Hz, 1H), 4.07 (s, 3H), 3.84 – 3.52 (m, 1H), 3.49 – 3.35 (m, 1H), 3.21 – 3.02 (m, 0H), 2.27 (d, J = 12.5 Hz, 2H), 2.08 (d, J = 13.2 Hz, 2H), 1.83 (q, J = 12.8 Hz, 2H), 1.49 (q, J = 11.6, 11.2 Hz, 2H), 1.18 (dd, J = 5.4, 1.6 Hz, 6H).
17	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.95 (s, 1H), 8.75 (d, J = 2.1 Hz, 1H), 8.67 (d, J = 2.1 Hz, 1H), 8.59 (s, 1H), 8.03 (d, J = 5.0 Hz, 1H), 7.95 (s, 1H), 7.87 – 7.51 (m, 2H), 7.21 (d, J = 5.1, 1.5 Hz, 1H), 4.57 – 4.32 (m, 1H), 4.06 – 3.84 (m, 2H), 3.60 – 3.41 (m, 1H), 2.97 – 2.75 (m, 1H), 2.43 – 2.25 (m, 2H), 2.26 – 2.18 (m, 2H), 1.87 – 1.72 (m, 2H), 1.70 – 1.58 (m, 2H), 1.29 (d, J = 1.6 Hz, 6H).
18	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.77 (d, J = 2.2 Hz, 1H), 8.71 (d, J = 2.2 Hz, 1H), 8.59 (s, 1H), 8.32 (s, 1H), 8.14 – 7.78 (m, 3H), 7.24 (d, J = 5.0 Hz, 1H), 4.45 (dd, J = 49.1, 8.4 Hz, 1H), 3.98 (dd, J = 23.8, 12.3 Hz, 1H), 3.57 – 3.44 (m, 2H), 3.04 – 2.91 (m, 1H), 2.36 – 2.24 (m, 4H), 1.76 (dd, J = 63.9, 12.5 Hz, 4H), 1.36 – 1.29 (m, 6H).
19	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.77 (d, J = 2.2 Hz, 1H), 8.70 (d, J = 2.2 Hz, 1H), 8.59 (s, 1H), 8.04 (d, J = 5.0 Hz, 1H), 7.96 (s, 1H), 7.77 (s, 1H), 7.23 (d, J = 5.1 Hz, 1H), 4.45 (ddd, J = 49.2, 9.4, 2.1 Hz, 1H), 4.10 (s, 3H), 4.02 – 3.86 (m, 1H), 3.55 – 3.44 (m, 2H), 2.88 (d, J = 3.5 Hz, 1H), 2.26 (dd, J = 36.9, 12.9 Hz, 4H), 1.90 – 1.52 (m, 4H), 1.35 – 1.25 (m, 6H).
20	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.78 (d, J = 2.2 Hz, 1H), 8.71 (d, J = 2.2 Hz, 1H), 8.59 (s, 1H), 8.05 (d, J = 5.1 Hz, 1H), 7.97 (s, 1H), 7.85 (s, 1H), 7.24 (d, J = 5.1 Hz, 1H), 4.45 (dd, J = 49.1, 7.5 Hz, 1H), 4.07 – 3.78 (m, 2H), 3.61 – 3.42 (m, 1H), 2.93 – 2.79 (m, 1H), 2.26 (dd, J = 39.3,

Compound	<sup>1</sup> H-NMR
	12.9 Hz, 4H), 1.73 (dd, J = 56.0, 12.8 Hz, 4H), 1.37 – 1.27 (m, 6H), 1.27 – 1.14 (m, 4H).
21	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.86 (d, J = 7.6 Hz, 1H), 8.75 (t, J = 1.8 Hz, 1H), 8.73 – 8.63 (m, 1H), 8.57 (d, J = 7.2 Hz, 1H), 8.02 (dd, J = 9.5, 5.1 Hz, 1H), 7.90 (d, J = 25.7 Hz, 1H), 7.61 (t, J = 59.0 Hz, 1H), 7.27 – 7.16 (m, 1H), 4.58 – 4.26 (m, 1H), 4.27 – 3.80 (m, 2H), 3.48 (tdd, J = 15.4, 9.3, 6.3 Hz, 1H), 3.16 – 2.80 (m, 1H), 2.27 (dd, J = 25.8, 13.3 Hz, 2H), 1.97 (ddd, J = 64.7, 24.1, 11.9 Hz, 5H), 1.70 – 1.52 (m, 1H), 1.28 (dd, J = 6.9, 1.7 Hz, 6H).
22	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.98 – 8.79 (m, 1H), 8.73 (t, J = 1.9 Hz, 1H), 8.66 (dd, J = 3.4, 2.0 Hz, 1H), 8.63 – 8.51 (m, 1H), 8.02 (dd, J = 8.4, 5.1 Hz, 1H), 7.88 (d, J = 2.4 Hz, 1H), 7.62 (td, J = 59.1, 2.9 Hz, 1H), 7.20 (d, J = 5.0 Hz, 1H), 4.42 (ddt, J = 49.0, 9.3, 2.7 Hz, 1H), 4.17 (q, J = 4.6, 4.2 Hz, 1H), 3.92 (ddt, J = 36.4, 14.5, 2.1 Hz, 1H), 3.70 – 3.38 (m, 2H), 3.06 (s, 1H), 2.27 (dd, J = 27.4, 13.4 Hz, 1H), 2.16 – 2.04 (m, 3H), 2.03 – 1.84 (m, 3H), 1.35 – 1.23 (m, 6H).; <sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.81 (d, J = 2.0 Hz, 1H), 8.64 – 8.49 (m, 3H), 8.06 (d, J = 2.1 Hz, 1H), 7.93 – 7.83 (m, 1H), 7.56 (td, J = 59.1, 2.1 Hz, 1H), 7.12 (dd, J = 5.0, 2.1 Hz, 1H), 4.42 (ddd, J = 48.9, 9.3, 2.3 Hz, 1H), 3.90 (ddd, J = 35.9, 14.5, 2.4 Hz, 1H), 3.74 (tq, J = 7.3, 4.3, 3.8 Hz, 1H), 3.59 – 3.43 (m, 1H), 2.91 (tt, J = 12.0, 3.6 Hz, 1H), 2.32 (dd, J = 12.8, 3.8 Hz, 2H), 2.23 (dd, J = 13.9, 3.6 Hz, 2H), 1.85 (qd, J = 13.2, 3.2 Hz, 2H), 1.57 (qd, J = 12.9, 3.2 Hz, 2H), 1.29 (d, J = 1.8 Hz, 6H).
23	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.75 (d, J = 2.3 Hz, 1H), 8.69 (d, J = 2.3 Hz, 1H), 8.58 (s, 1H), 8.06 (d, J = 5.0 Hz, 1H), 7.98 (s, 1H), 7.58 (d, J = 1.8 Hz, 1H), 7.33 – 6.89 (m, 2H), 6.63 – 6.52 (m, 1H), 4.57 – 4.30 (m, 2H), 4.07 – 3.82 (m, 2H), 3.65 – 3.43 (m, 1H), 2.47 – 2.21 (m, 4H), 2.13 (d, J = 13.0 Hz, 2H), 1.71 (q, J = 12.4 Hz, 2H), 1.29 (d, J = 1.7 Hz, 6H).; <sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> )

Compound	1H-NMR
	<p><math>\delta</math> 8.68 (d, J = 2.1 Hz, 1H), 8.59 (d, J = 1.7 Hz, 1H), 8.05 (dd, J = 5.1, 1.7 Hz, 1H), 7.94 (d, J = 1.7 Hz, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.21 (dd, J = 5.2, 1.6 Hz, 1H), 6.73 (td, J = 55.1, 1.7 Hz, 1H), 6.49 (d, J = 2.7 Hz, 1H), 4.58 – 4.26 (m, 2H), 4.08 – 3.80 (m, 2H), 3.61 – 3.42 (m, 1H), 2.39 – 2.30 (m, 2H), 2.25 (d, J = 11.0 Hz, 2H), 2.19 – 2.03 (m, 2H), 1.71 (qd, J = 12.9, 3.5 Hz, 2H), 1.29 (d, J = 1.7 Hz, 6H).</p>
24	<p>1H NMR (400 MHz, Methanol-d<sub>4</sub>) <math>\delta</math> 8.75 (t, J = 2.0 Hz, 1H), 8.68 (d, J = 2.2 Hz, 1H), 8.58 (d, J = 1.6 Hz, 1H), 8.35 (d, J = 1.7 Hz, 1H), 8.04 (d, J = 5.1 Hz, 1H), 7.94 (s, 2H), 7.21 (d, J = 5.2 Hz, 1H), 4.63 – 4.31 (m, 2H), 4.08 – 3.78 (m, 3H), 3.62 – 3.37 (m, 1H), 2.30 (dd, J = 25.8, 12.9 Hz, 4H), 2.15 (dd, J = 14.0, 11.1 Hz, 2H), 1.71 (q, J = 12.4 Hz, 2H), 1.29 (d, J = 1.8 Hz, 6H).</p>
25	<p>1H NMR (400 MHz, Methanol-d<sub>4</sub>) <math>\delta</math> 8.75 (d, J = 2.3 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.58 (s, 1H), 8.04 (d, J = 5.0 Hz, 1H), 7.95 (s, 1H), 7.76 – 7.65 (m, 1H), 7.51 – 7.32 (m, 1H), 7.22 (d, J = 5.1 Hz, 1H), 4.42 (ddd, J = 49.0, 9.3, 2.3 Hz, 1H), 4.32 – 4.15 (m, 1H), 4.07 – 3.80 (m, 2H), 3.49 (ddd, J = 16.1, 14.5, 9.3 Hz, 1H), 2.32 (d, J = 12.9 Hz, 2H), 2.23 (d, J = 13.2 Hz, 2H), 2.13 – 1.98 (m, 2H), 1.69 (q, J = 12.9 Hz, 2H), 1.29 (t, J = 1.7 Hz, 6H).</p>
26	<p>1H NMR (400 MHz, Methanol-d<sub>4</sub>) <math>\delta</math> 8.75 (d, J = 2.1 Hz, 1H), 8.70 (d, J = 2.2 Hz, 1H), 8.57 (s, 1H), 8.04 (d, J = 5.0 Hz, 1H), 7.96 (s, 1H), 7.47 (s, 1H), 7.32 (s, 1H), 7.22 (d, J = 5.0 Hz, 1H), 4.56 – 4.32 (m, 1H), 4.23 (t, J = 11.8 Hz, 1H), 4.07 – 3.82 (m, 2H), 3.49 (td, J = 15.0, 9.3 Hz, 1H), 2.31 (d, J = 12.8 Hz, 2H), 2.20 (d, J = 12.6 Hz, 2H), 2.08 (s, 4H), 2.04 (dd, J = 11.5, 1.9 Hz, 1H), 1.69 (q, J = 12.3 Hz, 2H), 1.29 (d, J = 1.7 Hz, 6H).</p>
27	<p>1H NMR (400 MHz, Methanol-d<sub>4</sub>) <math>\delta</math> 8.75 (t, J = 1.7 Hz, 1H), 8.69 (t, J = 1.8 Hz, 1H), 8.59 (d, J = 1.4 Hz, 1H), 8.12 – 8.02 (m, 1H), 7.96 (s, 1H), 7.76 (s, 1H), 7.52 (s, 1H), 7.22 (dd, J = 5.1, 1.4 Hz, 1H), 4.58 – 4.21 (m, 2H), 4.14 – 3.84 (m, 2H), 3.75 (s, 2H), 3.60 – 3.41</p>

Compound	1H-NMR
	(m, 1H), 2.32 (d, J = 12.9 Hz, 2H), 2.24 (d, J = 13.0 Hz, 2H), 2.18 – 2.06 (m, 2H), 1.81 – 1.61 (m, 2H), 1.29 (t, J = 1.4 Hz, 6 H).
28	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.75 (d, J = 2.3 Hz, 1H), 8.69 (d, J = 2.3 Hz, 1H), 8.58 (s, 1H), 8.06 (d, J = 5.0 Hz, 1H), 7.98 (s, 1H), 7.58 (d, J = 1.8 Hz, 1H), 7.33 – 6.89 (m, 2H), 6.63 – 6.52 (m, 1H), 4.57 – 4.30 (m, 2H), 4.07 – 3.82 (m, 2H), 3.65 – 3.43 (m, 1H), 2.47 – 2.21 (m, 4H), 2.13 (d, J = 13.0 Hz, 2H), 1.71 (q, J = 12.4 Hz, 2H), 1.29 (d, J = 1.7 Hz, 6H).; 1H NMR (400 MHz, Methanol-d4) $\delta$ 8.68 (d, J = 2.1 Hz, 1H), 8.59 (d, J = 1.7 Hz, 1H), 8.05 (dd, J = 5.1, 1.7 Hz, 1H), 7.94 (d, J = 1.7 Hz, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.21 (dd, J = 5.2, 1.6 Hz, 1H), 6.73 (td, J = 55.1, 1.7 Hz, 1H), 6.49 (d, J = 2.7 Hz, 1H), 4.58 – 4.26 (m, 2H), 4.08 – 3.80 (m, 2H), 3.61 – 3.42 (m, 1H), 2.39 – 2.30 (m, 2H), 2.25 (d, J = 11.0 Hz, 2H), 2.19 – 2.03 (m, 2H), 1.71 (qd, J = 12.9, 3.5 Hz, 2H), 1.29 (d, J = 1.7 Hz, 6H).
29	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.75 (d, J = 2.1 Hz, 1H), 8.67 (d, J = 2.1 Hz, 1H), 8.58 (s, 1H), 8.05 (d, J = 5.0 Hz, 1H), 7.91 (s, 1H), 7.31 – 6.58 (m, 4H), 4.56 – 4.29 (m, 2H), 4.15 – 3.81 (m, 2H), 3.49 (td, J = 15.2, 9.4 Hz, 1H), 2.48 – 2.24 (m, 4H), 2.15 (d, J = 12.5 Hz, 2H), 1.89 – 1.60 (m, 2H), 1.29 (d, J = 1.6 Hz, 6H).
30	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.75 (d, J = 2.1 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.58 (s, 1H), 8.18 (s, 1H), 8.04 (d, J = 5.1 Hz, 1H), 7.95 (s, 1H), 7.80 (s, 1H), 7.22 (d, J = 5.1 Hz, 1H), 4.60 – 4.23 (m, 2H), 4.14 – 3.81 (m, 2H), 3.59 – 3.40 (m, 1H), 2.46 – 2.21 (m, 4H), 2.14 (dt, J = 14.1, 11.4 Hz, 2H), 1.83 – 1.63 (m, 2H), 1.29 (d, J = 1.6 Hz, 6H).
31	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.75 (d, J = 2.2 Hz, 1H), 8.69 (d, J = 2.1 Hz, 1H), 8.62 (s, 1H), 8.09 – 8.05 (m, 2H), 7.96 (s, 1H), 7.77 (d, J = 1.0 Hz, 1H), 7.22 (d, J = 5.0 Hz, 1H), 4.71 (tt, J = 11.8, 3.8 Hz, 1H), 4.44 (ddd, J = 49.0, 9.3, 2.1 Hz, 1H), 4.10 – 4.01 (m, 1H), 3.93 (ddd, J = 36.5, 14.6, 2.2 Hz, 1H), 3.52 (ddd, J = 16.1, 14.5, 9.4 Hz, 1H), 2.44 – 2.30 (m,

Compound	1H-NMR
	4H), 2.30 – 2.12 (m, 2H), 1.89 – 1.67 (m, 2H), 1.30 (d, J = 1.7 Hz, 6H).
32	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.76 (d, J = 2.1 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.59 (s, 1H), 8.05 (d, J = 5.1 Hz, 1H), 7.94 (s, 1H), 7.76 (s, 1H), 7.23 (d, J = 5.1 Hz, 1H), 4.58 (tt, J = 11.6, 3.7 Hz, 1H), 4.43 (ddd, J = 49.0, 9.3, 2.1 Hz, 1H), 4.06 – 3.82 (m, 2H), 3.58 – 3.40 (m, 1H), 2.34 (t, J = 12.5 Hz, 4H), 2.24 – 2.09 (m, 2H), 1.98 (tt, J = 8.5, 5.1 Hz, 1H), 1.84 – 1.65 (m, 2H), 1.30 (d, J = 1.7 Hz, 6H), 1.05 – 0.94 (m, 2H), 0.83 – 0.71 (m, 2H).j
33	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.76 (d, J = 2.2 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.60 (s, 1H), 8.07 – 8.02 (m, 2H), 7.95 (s, 1H), 7.23 (d, J = 5.1 Hz, 1H), 5.16 – 4.93 (m, 2H), 4.85 – 4.80 (m, 2H), 4.73 – 4.57 (m, 1H), 4.54 – 4.32 (m, 2H), 4.12 – 3.76 (m, 2H), 3.64 – 3.40 (m, 1H), 2.47 – 2.31 (m, 4H), 2.21 (q, J = 11.6 Hz, 2H), 1.76 (q, J = 11.9 Hz, 2H), 1.30 (d, J = 1.6 Hz, 6H).
34	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.76 (d, J = 2.2 Hz, 1H), 8.70 (d, J = 2.2 Hz, 1H), 8.59 (s, 1H), 8.44 (s, 1H), 8.06 (d, J = 5.1 Hz, 1H), 7.95 (s, 1H), 7.23 (d, J = 5.0 Hz, 1H), 4.80 – 4.67 (m, 1H), 4.44 (ddd, J = 49.1, 9.4, 2.1 Hz, 1H), 4.12 – 3.81 (m, 2H), 3.62 – 3.43 (m, 1H), 2.38 (d, J = 11.3 Hz, 4H), 2.29 – 2.15 (m, 2H), 1.87 – 1.67 (m, 2H), 1.30 (d, J = 1.8 Hz, 6H).
35	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.77 (t, J = 1.8 Hz, 1H), 8.72 – 8.66 (m, 1H), 8.60 (d, J = 1.5 Hz, 1H), 8.39 (d, J = 1.6 Hz, 1H), 8.06 (d, J = 5.1 Hz, 1H), 7.95 (s, 1H), 7.30 – 7.18 (m, 1H), 6.98 (t, J = 54.6 Hz, 1H), 4.74 (t, J = 12.4 Hz, 1H), 4.58 – 4.31 (m, 1H), 4.18 – 3.75 (m, 2H), 3.51 (td, J = 15.1, 9.3 Hz, 1H), 2.39 (d, J = 11.6 Hz, 4H), 2.30 – 2.15 (m, 2H), 1.87 – 1.64 (m, 2H), 1.30 (d, J = 1.6 Hz, 6H).
36	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.75 (d, J = 2.3 Hz, 1H), 8.68 (d, J = 2.4 Hz, 1H), 8.60 (dd, J = 8.9, 2.4 Hz, 2H), 8.05 (t, J = 3.8 Hz, 1H), 7.93 (d, J = 2.5 Hz, 1H), 7.22 (t, J = 3.8 Hz, 1H), 7.03 – 6.54 (m, 1H), 4.62 –

Compound	<sup>1</sup> H-NMR
	4.28 (m, 2H), 4.10 – 3.81 (m, 2H), 3.62 – 3.41 (m, 1H), 2.33 (t, J = 14.2 Hz, 4H), 2.18 (q, J = 12.8 Hz, 2H), 1.73 (q, J = 12.3 Hz, 2H), 1.29 (t, J = 1.6 Hz, 6H).
37	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.75 (d, J = 2.3 Hz, 1H), 8.67 (d, J = 2.3 Hz, 1H), 8.58 (s, 1H), 8.06 (d, J = 4.8 Hz, 2H), 7.91 (s, 1H), 7.45 – 6.96 (m, 2H), 4.67 (t, J = 11.9 Hz, 1H), 4.56 – 4.26 (m, 1H), 4.11 – 3.85 (m, 2H), 3.60 – 3.43 (m, 1H), 2.33 (d, J = 11.0 Hz, 4H), 2.16 (d, J = 12.5 Hz, 2H), 1.73 (q, J = 12.7 Hz, 2H), 1.29 (d, J = 1.8 Hz, 6H).
38	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 9.33 (s, 1H), 8.62 (s, 1H), 8.59 (d, J = 2.2 Hz, 1H), 8.56 (d, J = 2.3 Hz, 1H), 8.27 (s, 1H), 7.84 (d, J = 4.8 Hz, 1H), 7.11 (d, J = 4.9 Hz, 1H), 5.51 (s, 2H), 4.85 – 4.73 (m, 1H), 4.46 (ddd, J = 48.9, 9.1, 2.3 Hz, 1H), 3.91 (ddd, J = 35.5, 14.5, 2.4 Hz, 1H), 3.76 (td, J = 11.4, 9.5, 4.2 Hz, 1H), 3.52 (ddd, J = 16.4, 14.4, 9.2 Hz, 1H), 3.37 (s, 1H), 2.45 (t, J = 12.0 Hz, 4H), 2.31 – 2.10 (m, 2H), 1.79 – 1.60 (m, 2H), 1.32 (d, J = 1.6 Hz, 6H).
39	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.74 (d, J = 2.2 Hz, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.58 (s, 1H), 8.03 (d, J = 5.0 Hz, 1H), 7.91 (s, 1H), 7.21 (d, J = 5.1 Hz, 1H), 4.42 (ddd, J = 49.1, 9.3, 2.1 Hz, 1H), 4.07 – 3.82 (m, 2H), 3.63 – 3.40 (m, 1H), 3.11 – 2.99 (m, 1H), 2.52 (s, 3H), 2.40 – 2.21 (m, 4H), 1.97 – 1.79 (m, 2H), 1.79 – 1.53 (m, 2H), 1.29 (d, J = 1.6 Hz, 6H).
40	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.74 (d, J = 2.2 Hz, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.60 (s, 1H), 8.04 (d, J = 5.1 Hz, 1H), 7.92 (s, 1H), 7.20 (d, J = 5.1 Hz, 1H), 4.43 (ddd, J = 49.1, 9.4, 2.1 Hz, 1H), 4.12 – 3.82 (m, 2H), 3.63 – 3.45 (m, 1H), 3.30 (p, J = 1.7 Hz, 2H), 3.11 (ddd, J = 12.0, 8.6, 3.4 Hz, 1H), 2.49 – 2.25 (m, 4H), 2.01 – 1.76 (m, 2H), 1.76 – 1.56 (m, 2H), 1.29 (d, J = 1.7 Hz, 6H).
41	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.75 (d, J = 2.2 Hz, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.58 (s, 1H), 8.03 (d, J = 5.1 Hz, 1H), 7.91 (s, 1H), 7.21 (d, J = 5.1 Hz, 1H), 4.42 (ddd, J = 49.1, 9.4, 2.1 Hz, 1H), 4.08 – 3.79 (m, 2H), 3.49 (td, J = 15.2, 9.4 Hz, 1H), 3.08 – 2.95 (m, 1H), 2.40 – 2.24 (m, 4H),

Compound	<sup>1</sup> H-NMR
	2.19 (tt, J = 8.4, 5.0 Hz, 1H), 1.94 – 1.78 (m, 2H), 1.76 – 1.56 (m, 2H), 1.29 (d, J = 1.7 Hz, 6H), 1.24 – 1.16 (m, 2H), 1.11 – 1.03 (m, 2H).
42	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.75 (d, J = 2.2 Hz, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.58 (s, 1H), 8.03 (d, J = 5.0 Hz, 1H), 7.91 (s, 1H), 7.21 (d, J = 5.1 Hz, 1H), 7.14 (t, J = 51.6 Hz, 1H), 4.42 (ddd, J = 49.0, 9.4, 2.1 Hz, 1H), 4.12 - 3.79 (m, 2H), 3.63 - 3.41 (m, 1H), 3.26 - 3.12 (m, 1H), 2.47 - 2.20 (m, 4H), 2.04 - 1.84 (m, 2H), 1.76 - 1.60 (m, 2H), 1.29 (d, J = 1.6 Hz, 6H).
43	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.75 (d, J = 2.2 Hz, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.60 (s, 1H), 8.03 (d, J = 5.0 Hz, 1H), 7.91 (s, 1H), 7.45 – 7.02 (m, 2H), 4.43 (ddd, J = 48.9, 9.3, 2.1 Hz, 1H), 4.17 – 4.04 (m, 1H), 4.02 – 3.82 (m, 1H), 3.64 – 3.38 (m, 1H), 2.72 – 2.51 (m, 2H), 2.48 – 2.15 (m, 4H), 2.06 – 1.86 (m, 2H), 1.29 (d, J = 1.6 Hz, 6H).
44	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.78 (d, J = 2.2 Hz, 1H), 8.70 (d, J = 2.2 Hz, 1H), 8.60 (s, 1H), 8.06 (d, J = 5.0 Hz, 1H), 7.95 (s, 1H), 7.24 (d, J = 5.0 Hz, 1H), 4.45 (ddd, J = 49.1, 9.4, 2.1 Hz, 1H), 4.12 – 3.83 (m, 2H), 3.65 – 3.44 (m, 1H), 2.94 (s, 1H), 2.61 (s, 3H), 2.32 (d, J = 12.7 Hz, 2H), 2.23 (d, J = 13.7 Hz, 2H), 1.88 (s, 2H), 1.73 – 1.59 (m, 2H), 1.32 (d, J = 1.6 Hz, 6H).
45	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.74 (d, J = 2.2 Hz, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.57 (s, 1H), 8.03 (d, J = 5.1 Hz, 1H), 7.90 (s, 1H), 7.21 (d, J = 5.1 Hz, 1H), 4.42 (ddd, J = 49.1, 9.3, 2.1 Hz, 1H), 4.09 – 3.83 (m, 2H), 3.64 – 3.41 (m, 1H), 3.18 – 3.06 (m, 1H), 2.36 (s, 3H), 2.35 – 2.23 (m, 4H), 2.01 – 1.82 (m, 2H), 1.73 – 1.58 (m, 2H), 1.29 (d, J = 1.7 Hz, 6H).
46	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.63 – 8.49 (m, 3H), 8.29 – 8.07 (m, 2H), 7.82 (dd, J = 5.7, 2.5 Hz, 1H), 7.08 (d, J = 4.9 Hz, 1H), 6.98 – 6.56 (m, 1H), 4.64 – 4.46 (m, 1H), 4.43 – 4.30 (m, 1H), 4.02 – 3.79 (m, 1H), 3.78 – 3.58 (m, 1H), 3.48 (td, J = 16.2, 15.6, 8.6 Hz, 1H), 2.99 (dd, J = 13.8, 9.0 Hz, 1H), 2.31 (dd, J = 29.0, 13.0 Hz, 3H), 1.86 (q, J = 12.9 Hz, 2H), 1.66 – 1.43 (m, 1H), 1.36 – 1.

Compound	1H-NMR
	25 (m, 6H).; 1H NMR (400 MHz, Methanol-d4) $\delta$ 8.75 (d, J = 2.2 Hz, 1H), 8.66 (d, J = 2.2 Hz, 1H), 8.59 (s, 1H), 8.21 – 8.08 (m, 1H), 8.01 (d, J = 5.1 Hz, 1H), 7.87 (d, J = 2.9 Hz, 1H), 7.21 (d, J = 5.1 Hz, 1H), 6.76 (t, J = 54.3 Hz, 1H), 4.41 (ddd, J = 49.1, 9.3, 2.2 Hz, 1H), 4.16 (s, 1H), 4.05 – 3.82 (m, 1H), 3.48 (td, J = 15.8, 15.4, 9.4 Hz, 1H), 3.14 (d, J = 11.6 Hz, 1H), 2.21 – 1.85 (m, 10H), 1.27 (d, J = 1.8 Hz, 6H).
47	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.77 (d, J = 2.2 Hz, 1H), 8.70 (d, J = 2.1 Hz, 1H), 8.60 (s, 1H), 8.06 (d, J = 5.1 Hz, 1H), 7.92 (s, 1H), 7.24 (d, J = 5.1 Hz, 1H), 6.93 (t, J = 53.7 Hz, 1H), 6.51 (s, 1H), 4.45 (ddd, J = 49.0, 9.4, 2.2 Hz, 1H), 4.08 – 3.81 (m, 2H), 3.63 – 3.42 (m, 1H), 3.11 – 2.99 (m, 1H), 2.49 – 2.19 (m, 4H), 1.95 – 1.77 (m, 2H), 1.75 – 1.60 (m, 2H), 1.32 (d, J = 1.7 Hz, 6H).
48	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.77 (d, J = 2.2 Hz, 1H), 8.74 (d, J = 1.8 Hz, 1H), 8.68 (d, J = 2.3 Hz, 1H), 8.15 - 7.89 (m, 2H), 7.23 (dd, J = 5.3, 1.8 Hz, 1H), 5.29 (t, J = 3.8 Hz, 1H), 4.44 (ddd, J = 49.0, 9.4, 2.3 Hz, 1H), 4.08 - 3.79 (m, 3H), 3.56 (d, J = 1.7 Hz, 3H), 1.29 (d, J = 1.9 Hz, 6H).
49	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.90 (s, 1H), 8.74 (d, J = 2.1 Hz, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.62 (s, 0H), 8.57 (s, 1H), 8.03 (d, J = 5.1 Hz, 1H), 7.88 (s, 1H), 7.73 (s, 1H), 7.21 (d, J = 5.1 Hz, 1H), 4.49 (dd, J = 9.4, 2.1 Hz, 1H), 4.36 (dd, J = 9.3, 2.1 Hz, 1H), 4.27 (s, 0H), 3.95 (s, 0H), 3.49 (dd, J = 9.4, 1.5 Hz, 0H), 3.11 (s, 0H), 2.22 (s, 1H), 2.05 (t, J = 14.9 Hz, 1H), 1.81 (q, J = 12.3 Hz, 2H), 1.73 - 1.59 (m, 2H), 1.43 (d, J = 10.3 Hz, 0H), 1.29 (d, J = 1.7 Hz, 6H).
50	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.31 (s, 1H), 8.01 (s, 1H), 7.97 – 7.69 (m, 2H), 7.28 (d, J = 5.2 Hz, 1H), 7.14 (s, 1H), 6.81 (s, 1H), 6.48 (s, 1H), 3.86 – 3.56 (m, 1H), 3.53 (s, 1H), 3.36 – 3.04 (m, 1H), 2.79 (d, J = 14.0 Hz, 1H), 2.41 (s, 1H), 2.12 – 1.81 (m, 3H), 1.52 (dd, J = 29.9, 12.1 Hz, 1H), 1.33 (d, J = 19.4 Hz, 5H), 1.07 (s, 2H), 0.93 (s, 0H), 0.64 – 0.42 (m, 6H).

Compound	1H-NMR
51	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.74 (d, J = 2.2 Hz, 1H), 8.65 (d, J = 2.3 Hz, 1H), 8.61 (s, 1H), 7.99 (d, J = 5.1 Hz, 1H), 7.88 (s, 1H), 7.75 (s, 1H), 7.20 (d, J = 5.0 Hz, 1H), 7.11 - 6.77 (m, 1H), 4.55 - 4.34 (m, 1H), 4.27 (s, 1H), 3.95 (dd, J = 36.4, 14.6 Hz, 1H), 3.52 (td, J = 14.2, 13.4, 8.3 Hz, 1H), 3.24 (s, 1H), 2.06 (dt, J = 30.8, 13.8 Hz, 6H), 1.84 (d, J = 12.0 Hz, 2H), 1.29 (d, J = 1.8 Hz, 6H).
52	-
53	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.75 (d, J = 2.1 Hz, 1H), 8.68 (d, J = 2.2 Hz, 1H), 8.58 (s, 1H), 8.04 (d, J = 5.1 Hz, 1H), 7.91 (s, 1H), 7.48 - 7.06 (m, 2H), 4.58 - 4.31 (m, 1H), 4.15 - 3.82 (m, 2H), 3.60 - 3.36 (m, 2H), 2.59 - 2.21 (m, 4H), 2.07 - 1.87 (m, 2H), 1.81 - 1.61 (m, 2H), 1.29 (d, J = 1.4 Hz, 6H).
54	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.85 - 8.77 (m, 1H), 8.75 (d, J = 2.2 Hz, 1H), 8.71 (d, J = 5.6 Hz, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.60 (s, 1H), 8.58 - 8.50 (m, 1H), 8.12 - 7.90 (m, 3H), 7.22 (d, J = 5.0 Hz, 1H), 4.49 (dd, J = 9.4, 2.1 Hz, 0H), 4.37 (dd, J = 9.4, 2.2 Hz, 0H), 4.08 - 3.79 (m, 2H), 3.60 - 3.42 (m, 0H), 2.99 (s, 0H), 2.35 (s, 1H), 2.14 (d, J = 13.1 Hz, 2H), 1.89 (d, J = 13.1 Hz, 1H), 1.71 (s, 1H), 1.28 (dd, J = 13.1, 1.7 Hz, 6H).
55	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.75 (d, J = 2.2 Hz, 1H), 8.68 (d, J = 2.2 Hz, 1H), 8.62 (d, J = 6.8 Hz, 2H), 8.25 (dd, J = 8.6, 6.9 Hz, 1H), 8.12 - 7.91 (m, 3H), 7.73 - 7.58 (m, 1H), 7.21 (d, J = 5.0 Hz, 1H), 6.77 (s, 1H), 4.45 (dd, J = 9.4, 2.2 Hz, 1H), 4.33 (dd, J = 9.3, 2.1 Hz, 0H), 4.02 - 3.75 (m, 1H), 3.48 (td, J = 15.6, 9.8 Hz, 1H), 3.12 (s, 0H), 2.95 (d, J = 19.1 Hz, 1H), 2.79 (t, J = 18.6 Hz, 2H), 2.62 - 2.45 (m, 1H), 2.40 - 2.20 (m, 1H), 2.13 (p, J = 6.8 Hz, 1H), 1.94 (s, 0H), 1.62 - 1.35 (m, 0H), 1.26 (d, J = 1.7 Hz, 6H).
56	1H NMR (400 MHz, Methanol-d4) $\delta$ 8.84 - 8.70 (m, 3H), 8.70 - 8.62 (m, 2H), 8.05 (dd, J = 13.0, 5.5 Hz, 3H), 7.90 (s, 1H), 7.21 (d, J = 5.1 Hz, 1H), 4.60 - 4.23 (m, 2H), 3.92 (ddd, J = 36.1, 14.5, 2.2 Hz, 1H), 3.76 - 3.52 (m, 1H), 3.44 (t, J = 7.1 Hz, 1H), 3.23 - 3.05 (m, 2H), 2.35 (t, J = 8.1

Compound	<sup>1</sup> H-NMR
	Hz, 1H), 2.25 - 2.11 (m, 2H), 2.10 - 1.96 (m, 5H), 1.86 (q, J = 13.0 Hz, 2H), 1.30 (d, J = 1.6 Hz, 6H).
57	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 9.05 (s, 1H), 8.80 (s, 2H), 8.74 (d, J = 2.1 Hz, 1H), 8.70 - 8.63 (m, 2H), 8.59 (s, 0H), 8.02 (dd, J = 8.1, 5.0 Hz, 1H), 7.91 (d, J = 18.6 Hz, 1H), 7.21 (dd, J = 5.1, 2.0 Hz, 1H), 4.50 (td, J = 8.8, 2.2 Hz, 1H), 4.46 - 4.29 (m, 1H), 4.09 - 3.82 (m, 1H), 3.54 (dddd, J = 31.1, 16.1, 14.5, 9.4 Hz, 1H), 2.85 (d, J = 29.2 Hz, 1H), 2.34 (d, J = 12.6 Hz, 1H), 2.24 - 1.75 (m, 6H), 1.73 - 1.59 (m, 1H), 1.40 - 1.21 (m, 6H).
58	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.75 (s, 1H), 8.66 (d, J = 4.1 Hz, 2H), 8.60 (d, J = 23.2 Hz, 1H), 8.01 (s, 0H), 7.90 (d, J = 16.2 Hz, 1H), 7.21 (d, J = 5.1 Hz, 1H), 4.50 (td, J = 8.8, 2.2 Hz, 1H), 4.46 - 4.29 (m, 1H), 4.09 - 3.82 (m, 1H), 3.54 (dddd, J = 31.1, 16.1, 14.5, 9.4 Hz, 1H), 2.85 (d, J = 29.2 Hz, 1H), 2.34 (d, J = 12.6 Hz, 1H), 2.24 - 1.75 (m, 6H), 1.73 - 1.59 (m, 1H), 2.67 (d, J = 2.2 Hz, 3H), 1.30 (d, J = 4.8 Hz, 6H).
59	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.89 (d, J = 2.7 Hz, 2H), 8.75 (d, J = 2.4 Hz, 1H), 8.72 - 8.63 (m, 1H), 8.11 - 7.97 (m, 1H), 7.91 (dd, J = 18.8, 2.6 Hz, 1H), 7.21 (dd, J = 5.1, 2.2 Hz, 1H), 7.08 - 6.83 (m, 1H), 6.66 (dd, J = 54.4, 3.3 Hz, 1H), 4.63 - 4.32 (m, 1H), 4.18 - 3.83 (m, 2H), 3.71 - 3.42 (m, 1H), 3.03 - 2.81 (m, 1H), 2.35 (d, J = 12.6 Hz, 1H), 2.22 - 1.78 (m, 7H), 1.69 (q, J = 12.3 Hz, 1H), 1.30 (dd, J = 5.1, 1.8 Hz, 6H).
60	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.81 - 8.69 (m, 2H), 8.56 (s, 1H), 8.36 (s, 1H), 7.95 (d, J = 5.1 Hz, 1H), 7.22 (d, J = 5.1 Hz, 1H), 4.41 (ddd, J = 49.1, 9.4, 2.1 Hz, 1H), 3.92 (ddd, J = 36.4, 14.6, 2.1 Hz, 1H), 3.63 - 3.39 (m, 1H), 2.52 (s, 3H), 2.25 (d, J = 4.8 Hz, 12H), 1.28 (d, J = 1.7 Hz, 6H).
61	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 9.38 (s, 1H), 8.80 - 8.73 (m, 2H), 8.56 (s, 1H), 8.39 (s, 1H), 7.95 (d, J = 5.1 Hz, 1H), 7.22 (d, J = 5.1 Hz, 1H), 4.58 - 4.27 (m, 1H), 3.92 (ddd, J = 36.6, 14.6, 2.1 Hz, 1H), 3.48 (td, J = 15.7, 9.4 Hz, 1H), 2.32 (s, 12H), 1.28 (d, J = 1.6 Hz, 6H).

Compound	<sup>1</sup> H-NMR
62	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.75 (d, J = 2.1 Hz, 2H), 8.58 (d, J = 2.1 Hz, 1H), 8.35 (s, 1H), 7.96 (d, J = 4.9 Hz, 1H), 7.29 – 6.92 (m, 2H), 4.41 (ddd, J = 49.1, 9.4, 2.2 Hz, 1H), 3.91 (ddd, J = 36.5, 14.6, 2.2 Hz, 1H), 3.49 (td, J = 15.1, 9.3 Hz, 1H), 2.30 (s, 12H), 1.28 (d, J = 1.8 Hz, 6H).
63	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.75 (d, J = 2.2 Hz, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.62 (s, 1H), 8.06 (d, J = 5.0 Hz, 1H), 7.95 (s, 1H), 7.44 – 7.02 (m, 2H), 5.02 (dd, J = 9.2, 3.6 Hz, 1H), 4.43 (ddd, J = 49.0, 9.1, 2.3 Hz, 1H), 4.30 – 4.14 (m, 2H), 3.94 (ddd, J = 36.4, 14.7, 2.7 Hz, 1H), 3.77 – 3.59 (m, 1H), 3.60 – 3.42 (m, 1H), 2.52 – 2.39 (m, 1H), 2.37 – 2.19 (m, 2H), 2.06 – 1.88 (m, 1H), 1.30 (q, J = 1.8 Hz, 6H).
64	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.75 (q, J = 2.2 Hz, 2H), 8.61 (s, 1H), 8.35 (s, 1H), 7.96 (d, J = 5.0 Hz, 1H), 7.22 (d, J = 5.1 Hz, 1H), 4.55 – 4.27 (m, 3H), 3.92 (ddd, J = 36.5, 14.6, 2.1 Hz, 1H), 3.49 (ddd, J = 16.0, 14.5, 9.4 Hz, 1H), 2.63 (t, J = 7.9 Hz, 2H), 2.55 (s, 3H), 2.51 – 2.30 (m, 6H), 1.28 (d, J = 1.6 Hz, 6H).
65	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.76 (d, J = 1.6 Hz, 2H), 8.62 (d, J = 1.1 Hz, 1H), 8.33 (s, 1H), 7.97 (d, J = 5.2 Hz, 1H), 7.22 (d, J = 5.2 Hz, 1H), 7.17 (t, J = 51.4 Hz, 1H), 4.58 - 4.30 (m, 3H), 4.04 - 3.80 (m, 1H), 3.60 - 3.42 (m, 1H), 2.67 (m, 2H), 2.47 (m, 6H), 1.29 (d, J = 1.4 Hz, 6H).
66	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.80 – 8.74 (m, 2H), 8.58 (s, 1H), 8.37 (s, 1H), 8.14 (s, 1H), 7.97 (d, J = 5.0 Hz, 1H), 7.25 (d, J = 5.1 Hz, 1H), 6.89 (s, 1H), 4.44 (ddd, J = 49.0, 9.4, 2.1 Hz, 1H), 3.95 (ddd, J = 36.8, 14.5, 2.1 Hz, 1H), 3.58 – 3.42 (m, 1H), 2.33 – 2.24 (m, 6H), 2.21 – 2.11 (m, 6H), 1.33 – 1.29 (m, 6H).
67	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.74 (d, J = 2.2 Hz, 1H), 8.65 (d, J = 2.2 Hz, 1H), 8.55 (s, 1H), 8.00 (d, J = 5.0 Hz, 1H), 7.85 (s, 1H), 7.20 (d, J = 5.0 Hz, 1H), 4.41 (ddd, J = 49.0, 9.3, 2.1 Hz, 1H), 4.07 – 3.84 (m, 3H), 3.84 – 3.71 (m, 1H), 3.57 – 3.43 (m, 1H), 3.40 (t, J = 11.0 Hz, 2H), 2.22

Compound	<sup>1</sup> H-NMR
	(d, J = 12.2 Hz, 2H), 1.96 (d, J = 12.1 Hz, 2H), 1.68 (d, J = 11.1 Hz, 2H), 1.53 – 1.15 (m, 14H).
68	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.76 (s, 2H), 8.60 (s, 1H), 8.33 (s, 1H), 7.95 (d, J = 5.1 Hz, 1H), 7.22 (d, J = 5.0 Hz, 1H), 4.40 (ddd, J = 49.1, 9.4, 2.1 Hz, 1H), 4.05 – 3.33 (m, 5H), 2.42 (d, J = 12.5 Hz, 4H), 2.33 (dd, J = 10.0, 5.0 Hz, 6H), 2.22 (dd, J = 9.9, 5.1 Hz, 6H), 1.28 (d, J = 1.7 Hz, 6H).
69	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.76 (t, J = 1.5 Hz, 2H), 8.54 (s, 1H), 8.41 (s, 1H), 7.92 (d, J = 5.1 Hz, 1H), 7.22 (d, J = 5.1 Hz, 1H), 4.40 (ddd, J = 49.0, 9.4, 2.1 Hz, 1H), 4.05 (s, 2H), 4.00 – 3.87 (m, 1H), 3.83 (dd, J = 6.0, 4.1 Hz, 2H), 3.57 – 3.42 (m, 3H), 2.40 (dd, J = 10.3, 5.3 Hz, 6H), 2.24 (dd, J = 10.3, 5.4 Hz, 6H), 1.28 (d, J = 1.7 Hz, 6H).

Example #	<sup>1</sup> H-NMR
70	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.78 (d, J = 2.2 Hz, 1H), 8.70 (d, J = 2.1 Hz, 1H), 8.61 (s, 1H), 8.06 (d, J = 5.1 Hz, 1H), 7.96 (s, 1H), 7.69 (d, J = 2.2 Hz, 1H), 7.24 (d, J = 5.0 Hz, 1H), 6.33 (d, J = 2.2 Hz, 1H), 4.46 (ddd, J = 49.1, 9.4, 2.1 Hz, 1H), 4.14 – 3.75 (m, 2H), 3.63 – 3.35 (m, 1H), 2.87 (ddt, J = 12.1, 7.5, 3.7 Hz, 1H), 2.32 (dd, J = 12.9, 3.7 Hz, 2H), 2.28 – 2.12 (m, 2H), 1.74 (dq, J = 65.3, 12.9, 3.2 Hz, 4H), 1.32 (d, J = 1.6 Hz, 7H).
71	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.78 (d, J = 2.1 Hz, 1H), 8.69 (d, J = 2.2 Hz, 1H), 8.64 (s, 1H), 8.04 (d, J = 5.1 Hz, 1H), 7.91 (s, 1H), 7.67 (d, J = 2.2 Hz, 1H), 7.24 (d, J = 5.0 Hz, 1H), 6.92 (dd, J = 6.3, 1.8 Hz, 2H), 6.34 (d, J = 2.2 Hz, 1H), 4.45 (ddd, J = 49.1, 9.4, 2.1 Hz, 1H), 4.27 (s, 1H), 4.09 – 3.89 (m, 2H), 3.79 (d, J = 11.6 Hz, 3H), 3.54 (ddd, J = 15.8, 14.4, 9.2 Hz, 1H), 2.99 (t, J = 10.6 Hz, 1H), 2.04 (q, J = 10.9, 9.8 Hz, 7H), 1.88 (d, J = 10.0 Hz, 1H), 1.31 (d, J = 1.6 Hz, 7H).

72	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.61 (s, 1H), 8.57 (q, J = 2.3 Hz, 2H), 8.28 (s, 1H), 8.18 (t, J = 57.0 Hz, 1H), 7.84 (d, J = 4.9 Hz, 1H), 7.11 (d, J = 4.9 Hz, 1H), 4.45 (ddd, J = 48.9, 9.1, 2.3 Hz, 1H), 3.90 (ddd, J = 35.5, 14.5, 2.3 Hz, 1H), 3.78 – 3.65 (m, 0H), 3.52 (ddd, J = 16.7, 14.6, 9.1 Hz, 1H), 2.44 (d, J = 12.8 Hz, 2H), 2.24 (d, J = 13.4 Hz, 2H), 2.04 (q, J = 12.2, 11.7 Hz, 2H), 1.60 (q, J = 12.4 Hz, 2H), 1.32 (d, J = 1.7 Hz, 6H).
73	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 9.05 (s, 1H), 8.78 (d, J = 2.2 Hz, 2H), 8.62 (d, J = 14.2 Hz, 2H), 8.05 (dd, J = 7.4, 5.1 Hz, 2H), 7.95 (s, 1H), 7.90 (s, 1H), 7.65 (d, J = 2.0 Hz, 2H), 7.24 (d, J = 5.1 Hz, 2H), 6.31 (dd, J = 8.5, 2.2 Hz, 2H), 4.45 (dd, J = 49.0, 9.3 Hz, 2H), 4.27 (s, 1H), 4.05 – 3.81 (m, 2H), 3.54 (td, J = 16.0, 8.2 Hz, 2H), 2.99 (d, J = 10.7 Hz, 1H), 2.87 (t, J = 12.0 Hz, 0H), 2.32 (d, J = 12.4 Hz, 2H), 2.20 (d, J = 13.4 Hz, 2H), 2.05 (d, J = 12.1 Hz, 4H), 1.83 (dt, J = 25.9, 11.7 Hz, 3H), 1.65 (q, J = 11.5, 11.1 Hz, 2H), 1.32 (dd, J = 4.1, 1.7 Hz, 11H).
74	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.75 (d, J = 2.2 Hz, 1H), 8.68 (d, J = 2.1 Hz, 1H), 8.62 (s, 1H), 8.06 (d, J = 5.1 Hz, 1H), 7.94 (s, 1H), 7.50 – 7.00 (m, 2H), 5.02 (dd, J = 9.3, 3.5 Hz, 1H), 4.55 – 4.34 (m, 1H), 4.32 – 4.14 (m, 2H), 4.07 – 3.85 (m, 1H), 3.66 (dd, J = 11.0, 8.4 Hz, 1H), 3.60 – 3.43 (m, 1H), 2.44 (d, J = 12.7 Hz, 1H), 2.39 – 2.19 (m, 2H), 2.07 – 1.89 (m, 1H), 1.30 (d, J = 1.6 Hz, 6H).
75	<sup>1</sup> H NMR (400 MHz, Methanol-d <sub>4</sub> ) δ 8.79 (d, J = 2.2 Hz, 1H), 8.72 (d, J = 2.2 Hz, 1H), 8.61 (s, 1H), 8.23 – 7.89 (m, 3H), 7.82 (s, 1H), 7.25 (d, J = 5.1 Hz, 1H), 4.60 – 4.32 (m, 1H), 4.10 – 3.71 (m, 2H), 3.63 – 3.43 (m, 1H), 3.24 – 3.08 (m, 1H), 2.29 (dd, J = 47.0, 12.9 Hz, 4H), 1.92 – 1.60 (m, 4H), 1.36 – 1.25 (m, 6H).

## BIOLOGICAL ASSAYS

Biological assays were conducted to measure activity against TNF $\alpha$  and IRAK4. As summarized in **Table 3**, the test compounds are inhibitors of IRAK4.

### 5 IRAK4 Monocyte TNF $\alpha$ Cell Based Assay Procedure:

Cryopreserved human monocytes (Stem Cell Technologies) were thawed, diluted in RPMI with GlutaMAX™ (Gibco® 200mM L-alanyl-L-glutamine) (10mM HEPES, 1X Pen-

Strep, 55  $\mu$ M  $\beta$ -mercaptoethanol, 1 mM Sodium pyruvate) media containing 10% FBS to 0.125 X10<sup>6</sup> cells/ml and recovered at 37°C for 2 hours. The cell suspension was then plated at a density of 5,000 cells/well onto black 384 well Greiner clear bottom plates. Plates were pre-spotted with test compounds and serially diluted in DMSO where 40 nL/well were delivered using the Echo 550 acoustic liquid dispenser (Labcyte®) for a final DMSO concentration of 0.1%. Plated cells were treated with compound for 1 hour at 37°C. Cells were then stimulated with 50 pg/ml of LPS (Sigma) excluding outside columns of plate used for unstimulated cell control wells. Cells were incubated for an additional 4 hours at 37°C. Cells were then spun out of the media and 5  $\mu$ l of sample were taken and analyzed for total TNF $\alpha$  content using the TR-FRET Human TNF $\alpha$  detection system (CisBio). This system utilizes two labeled antibodies (cryptate and XL665) that bind to two different epitopes of the TNF $\alpha$  molecule and produce FRET signal proportional to the concentration of TNF $\alpha$  in the sample. Detection antibodies are mixed 50:50 and 5  $\mu$ L were dispensed into each well. Plates were covered with clear seals and incubated at room temp overnight. The following morning plates were read using an Envision 2103 Multilabeled reader (PerkinElmer) with excitation/emission/FRET emission at 340 nm/615 nm/665 nm, respectively. Fluorescence intensities at 615 nm and 665 nm emission wavelengths were expressed as a ratio (665 nm/615 nm). Percent of control was calculated as follows:

$$\% \text{ Control} = 100 \times (\text{Ratio}_{\text{Sample}} - \text{Ratio}_{0\% \text{ Stimulation}}) / (\text{Ratio}_{100\% \text{ Stimulation}} - \text{Ratio}_{0\% \text{ Stimulation}})$$

where unstimulated cells (0% stimulation) were the negative control and stimulated cells (100% stimulation) were used as the positive control.

#### **IRAK4 Biochemical Assay Procedure:**

IRAK4 enzyme (Carna Biosciences, Chuo-ku, Kobe, Japan) activity was measured by detecting phosphorylated peptide substrate formation using an antibody against the phosphorylated peptide substrate. This is a time-resolved fluorescence resonance energy transfer (TR-FRET) immunoassay, based on the STK1 KinEASE Assay (Cisbio, Bedford, Massachusetts). The assay was designed as a simple two-step, endpoint assay (a 5  $\mu$ l enzyme reaction followed by 5 $\mu$ l stop and detect Solution) performed in ProxiPlate-384 Plus plates (Perkin Elmer, Waltham, Massachusetts). Staurosporine, a non-selective kinase inhibitor was used as a positive control. Compounds diluted in DMSO were spotted into 384 well plates using a Labcyte® Echo 550 Liquid Handling System prior to addition of IRAK4 enzyme and peptide substrate. Reaction solutions were delivered using a Multi-Flo (Bio-Tek Instruments). The enzyme and peptide solution was incubated with compound for 15 minutes at room temp before

the reaction was initiated by the addition of ATP. The standard 5 $\mu$ l reaction mixture contained 500  $\mu$ M ATP, 2  $\mu$ M peptide (STK1 Peptide), 0.75 nM of IRAK4 in reaction buffer (50 mM HEPES, pH 7.0, 0.02% NaN<sub>3</sub>, 0.01% BSA, 0.1 mM Orthovanadate, 5 mM MgCl<sub>2</sub>, 0.025% NP-40, 1mM DTT). After 120 min of incubation at room temperature, 5  $\mu$ l of Stop and Detect

5 Solution (1:100 Cryptate labeled anti-phosphorylated peptide antibody solution and 125 nM Tracer in a 50mM HEPES pH 7.0 detection buffer containing sufficient EDTA) was added. The plate was then further incubated for 60 minutes at room temperature and read on Envision 2103 Multilabeled reader (PerkinElmer) with excitation/emission/FRET emission at 340nm/615nm/665nm, respectively. Fluorescence intensities at 615nm and 665nm emission

10 wavelengths were expressed as a ratio (665nm/615nm). Percentage of inhibition was calculated as below:

$$\% \text{ Inhibition} = 100 \times (\text{Ratio}_{\text{Sample}} - \text{Ratio}_{0\% \text{ Inhibition}}) / (\text{Ratio}_{100\% \text{ Inhibition}} - \text{Ratio}_{0\% \text{ Inhibition}})$$

The 0% inhibition value comes from control wells lacking inhibitor. The 100% inhibition value comes from control wells containing a saturating amount of known inhibitor

15 staurosporine.

**Table 3**

<b>Compound</b>	<b>EC50 TNF(nM)</b>	<b>IC50 HTRF (nM)</b>
1	4	<1
2	66	<1
3	9	<1
4	37	3
5	22	<1
6	70	-
7	18	1
8	36	1
9	114	7
10	55	8
11	17	1

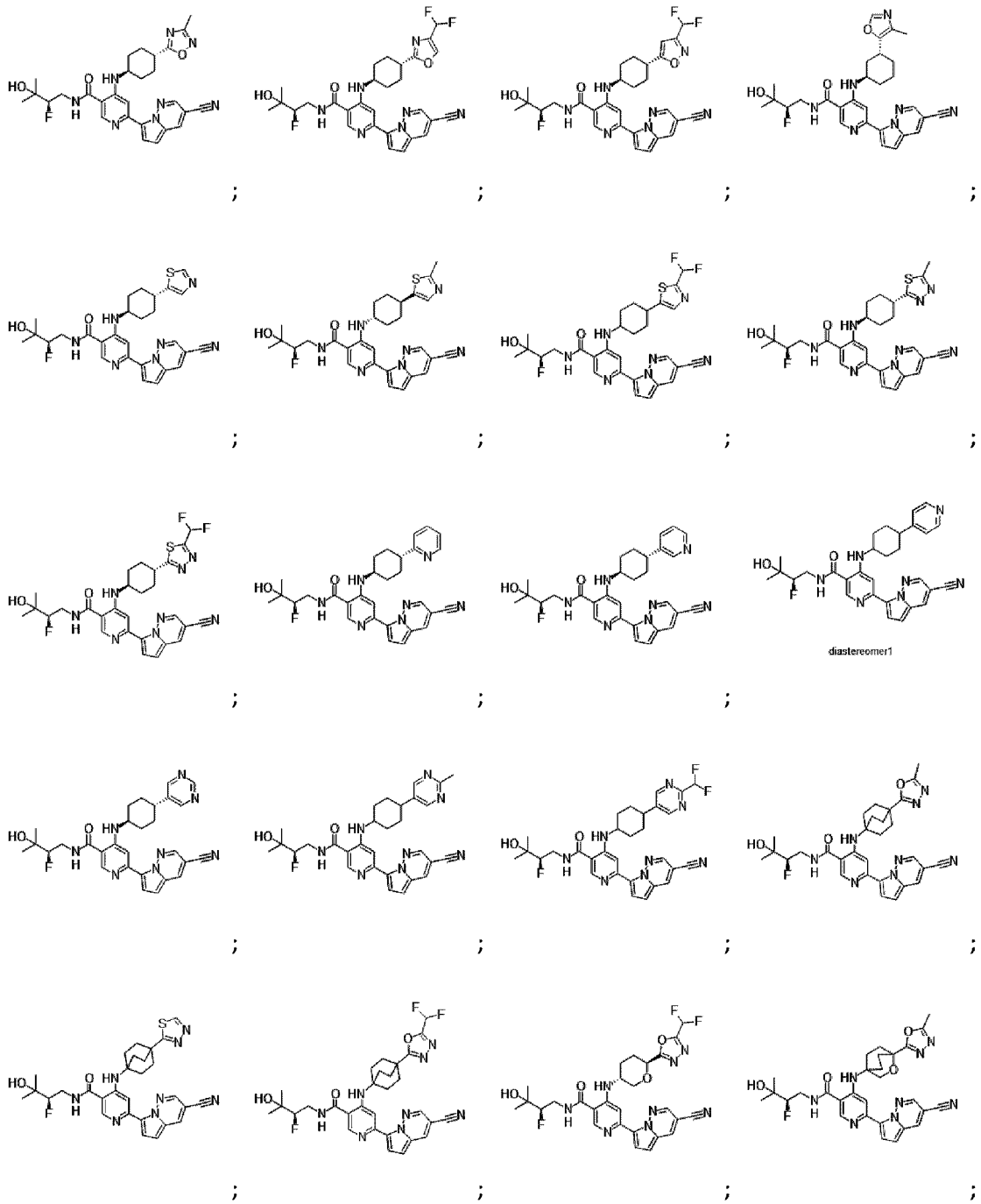
<b>Compound</b>	<b>EC50 TNF(nM)</b>	<b>IC50 HTRF (nM)</b>
12	44	2
13	169	2
14	53	1
15	35	<1
16	26	<1
17	33	1
18	27	1
19	26	<1
20	49	1
21	60	2
22	67	2
23	38	1
24	19	<1
25	29	2
26	91	<1
27	58	<1
28	187	2
29	381	7
30	136	4
31	40	1
32	63	1
33	200	1
34	43	<1

<b>Compound</b>	<b>EC50 TNF(nM)</b>	<b>IC50 HTRF (nM)</b>
35	16	<1
36	14	<1
37	40	1
38	24	<1
39	33	<1
40	66	1
41	38	<1
42	24	<1
43	39	<1
44	28	<1
45	85	2
46	124	2
47	89	2
48	1050	10
49	13	<1
50	52	1
51	76	3
52	50	1
53	27	<1
54	18	<1
55	25	<1
56	221	9
57	11	2

<b>Compound</b>	<b>EC50 TNF(nM)</b>	<b>IC50 HTRF (nM)</b>
58	112	4
59	21	1
60	15	<1
61	4	<1
62	19	<1
63	39	<1
64	19	<1
65	23	1
66	8	<1
67	41	1
68	38	<1
69	15	<1
70	27.198	0.822
71	205.76	3.129
72	31.321	0.639
73		
74	71.436	0.868
75	14.802	0.875

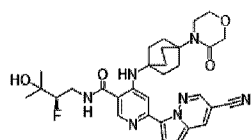
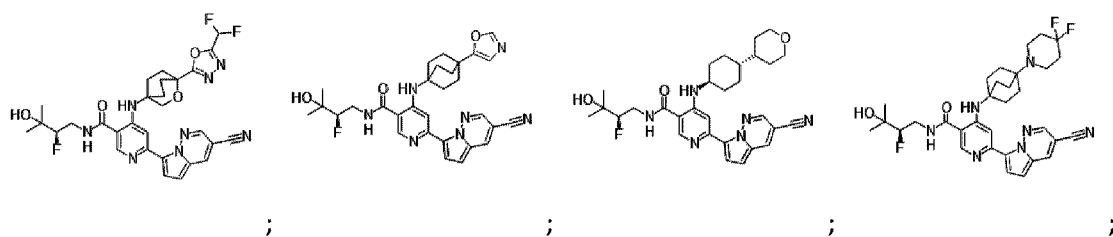




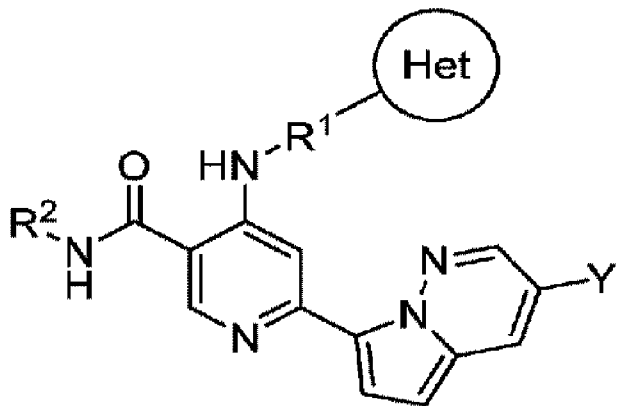


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and



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