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(19) **United States**(12) **Patent Application Publication****Liu et al.**(10) **Pub. No.: US 2015/0011508 A1**(43) **Pub. Date: Jan. 8, 2015**(54) **COMPOUNDS AND COMPOSITIONS AS C-KIT KINASE INHIBITORS**(75) Inventors: **Xiaodong Liu**, San Diego, CA (US); **Xiaolin Li**, Alameda, CA (US); **Jon Loren**, San Diego, CA (US); **Valentina Molteni**, San Diego, CA (US); **Juliet Nabakka**, San Diego, CA (US); **Bao Nguyen**, San Diego, CA (US); **Hank Michael James Petrassi**, Cardiff, CA (US); **Vince Yeh**, San Diego, CA (US)(73) Assignee: **IRM LLC**, Hamilton (BM)(21) Appl. No.: **14/241,883**(22) PCT Filed: **Aug. 28, 2012**(86) PCT No.: **PCT/US2012/052704**

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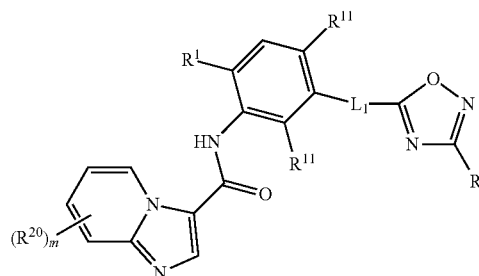
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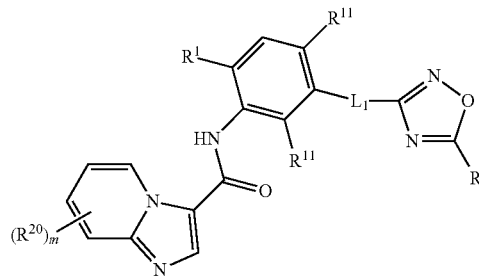
**Publication Classification**(51) **Int. Cl.****C07D 471/04** (2006.01)**C07F 9/6561** (2006.01)(52) **U.S. Cl.**CPC ..... **C07D 471/04** (2013.01); **C07F 9/6561** (2013.01)USPC ..... **514/80**; 546/121; 514/300; 544/127; 514/233.2; 546/23; 544/362; 514/253.04(57) **ABSTRACT**

The invention provides compounds of formulae (I) and (II) and pharmaceutical compositions thereof, which are useful as protein kinase inhibitors, as well as methods for using such compounds to treat, ameliorate or prevent a condition associated with abnormal or deregulated kinase activity. In some embodiments, the invention provides methods for using such compounds to treat, ameliorate or prevent diseases or disorders that involve abnormal activation of c-kit or c-kit and PDGFR (PDGFR $\alpha$ , PDGFR $\beta$ ) kinases.

Formula (I)



Formula (II)



COMPOUNDS AND COMPOSITIONS AS  
C-KIT KINASE INHIBITORS

FIELD OF THE INVENTION

[0001] The invention relates to inhibitors of PDGFR and/or c-kit kinases, and methods of using such compounds.

BACKGROUND OF THE INVENTION

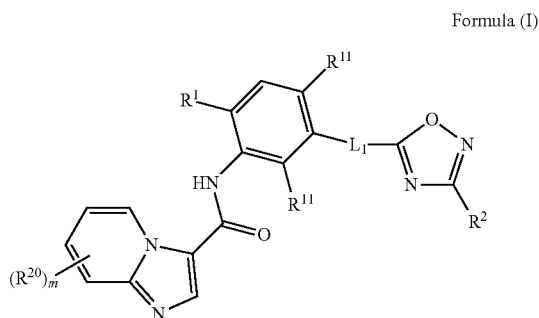
[0002] Protein kinases (PK) are a large set of structurally related phosphoryl transferases having highly conserved structures and catalytic functions. Protein kinases are enzymatic components of the signal transduction pathways which catalyze the transfer of the terminal phosphate from ATP to the hydroxy group of tyrosine, serine and/or threonine residues of proteins, and are therefore categorized into families by the substrates they phosphorylate: Protein Tyrosine Kinases (PTK), and Protein Serine/Threonine Kinases.

[0003] Protein kinases play a critical role in the control of cell growth and differentiation and are responsible for the control of a wide variety of cellular signal transduction processes, wherein protein kinases are key mediators of cellular signals leading to the production of growth factors and cytokines. The overexpression or inappropriate expression of normal or mutant protein kinases plays a significant role in the development of many diseases and disorders including, central nervous system disorders such as Alzheimer's, inflammatory disorders such as arthritis, bone diseases such as osteoporosis, metabolic disorders such as diabetes, blood vessel proliferative disorders such as angiogenesis, autoimmune diseases such as rheumatoid arthritis, ocular diseases, cardiovascular disease, atherosclerosis, cancer, thrombosis, psoriasis, restenosis, schizophrenia, pain sensation, transplant rejection and infectious diseases such as viral, and fungal infections.

SUMMARY OF THE INVENTION

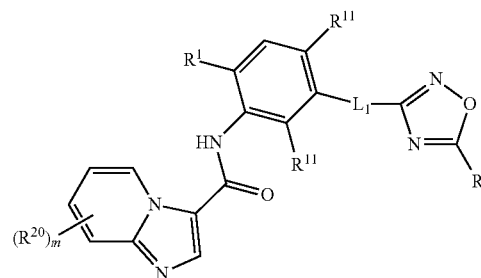
[0004] Provided herein are compounds, and pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, which are inhibitors of c-kit kinase, or inhibitors of c-kit and PDGFR (PDGFR $\alpha$  and PDGFR $\beta$ ) kinases.

[0005] In one aspect provided herein such compounds, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure according to Formula (I) or Formula (II):



-continued

Formula (II)



wherein:

[0006] m is 1 and R<sup>20</sup> is selected from H, halo, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>haloalkoxy, deuterium, deuterated C<sub>1</sub>-C<sub>6</sub>alkyl, —CN, —(CR<sup>9</sup>)<sub>n</sub>—OR<sup>4</sup>, —C(O)R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>—C(=O)OR<sup>4</sup>, R<sup>8</sup>, —(CR<sup>9</sup>)<sub>n</sub>—R<sup>8</sup>, —((CR<sup>9</sup>)<sub>n</sub>O)<sub>t</sub>R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>—R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>—C(=O)R<sup>4</sup>, —C(=O)N(R<sup>4</sup>)<sub>2</sub>, —N(R<sup>4</sup>)<sub>2</sub>, —C(=S)N(R<sup>4</sup>)<sub>2</sub>, —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —OR<sup>4</sup> and —(CR<sup>9</sup>)<sub>n</sub>CN,

[0007] or m is 4 and R<sup>20</sup> is deuterium;

[0008] R<sup>1</sup> is selected from C<sub>1</sub>-C<sub>6</sub>alkyl and halo;

[0009] each R<sup>11</sup> is independently selected from H, halo and C<sub>1</sub>-C<sub>6</sub>alkyl;

[0010] L<sub>1</sub> is a bond, —NH— or —C(O)NH—;

[0011] R<sup>2</sup> is selected from C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl, —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>S(=O)<sub>2</sub>NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>CN, —(CR<sup>9</sup>)<sub>n</sub>C(=O)R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>OC(=O)R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>C(=O)OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>C(=O)NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>OC(=O)NR<sup>4</sup>, (CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>OCR<sup>9</sup>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>CR<sup>9</sup>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>CR<sup>9</sup>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>CR<sup>9</sup>OC(O)(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>OC(O)(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>, —CR<sup>9</sup>R<sup>6</sup>, —CR<sup>9</sup>R<sup>6</sup>, —CR<sup>9</sup>NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>, —NR<sup>4</sup>(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —NR<sup>4</sup>(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —NR<sup>4</sup>(CR<sup>9</sup>)<sub>n</sub>R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)O(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —CR<sup>9</sup>R<sup>6</sup>NR<sup>4</sup>S(=O)<sub>2</sub>R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)O(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, and —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)O(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>;

[0012] each R<sup>4</sup> is independently selected from H and C<sub>1</sub>-C<sub>6</sub>alkyl;

[0013] each R<sup>5</sup> is independently selected from —NHC(O)OR<sup>4</sup>, —OR<sup>4</sup>, —OP(O)(OR<sup>4</sup>)<sub>2</sub> and —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>;

[0014] each R<sup>6</sup> is a C<sub>1</sub>-C<sub>6</sub>haloalkyl;

[0015] each R<sup>9</sup> is independently selected from H and C<sub>1</sub>-C<sub>6</sub>alkyl;

[0016] R<sup>8</sup> is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O

or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

[0017] wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl and substituted 4-6 membered heterocycloalkyl of R<sup>8</sup> are substituted with 1-3 substituents independently selected from C<sub>1</sub>-C<sub>6</sub>alkyl, halo,  $-(C(R^9)_2)_nOR^4$ ,  $-C(O)NR^4$ ,  $-NR^4$ ,  $-R^{10}$ ,  $-(C(R^9)_2)_nR^{10}$ ,  $-OR^4$ ,  $-(C(R^9)_2)_nC(O)OR^4$ ,  $-C(O)OR^4$ ,  $-(C(R^9)_2)_nC(O)NR^4$ ,  $-C(O)NR^4(C(R^9)_2)_nR^{10}$ ,  $-(C(R^9)_2)_nC(O)NR^4(C(R^9)_2)_nR^{10}$ ,  $-(C(R^9)_2)_nC(O)NR^4(C(R^9)_2)_nOR^4$ ,  $-C(O)NR^4(C(R^9)_2)_nOR^4$ ,  $-C(O)OR^4$ ,  $-C(O)R^4$  and  $-S(O)_2R^4$ ;

[0018] R<sup>10</sup> is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, and a substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl,

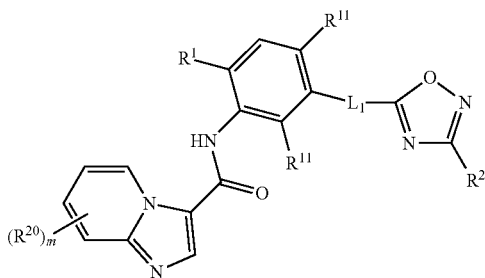
[0019] wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl and substituted 4-6 membered heterocycloalkyl of R<sup>10</sup> are substituted with 1-3 substituents independently selected from C<sub>1</sub>-C<sub>6</sub>alkyl, and  $-(C(R^9)_2)_nOR^4$ ;

[0020] t is 1, 2 or 3, and

[0021] each n is independently selected from 1, 2, 3 and 4.

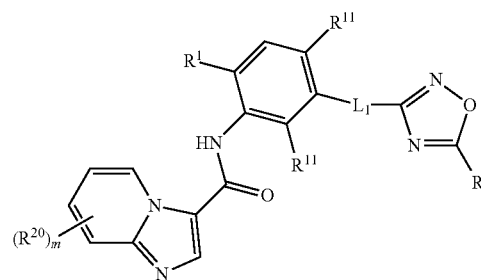
[0022] In certain embodiments of compounds of Formula (I) or Formula (II), and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof,

Formula (I)



-continued

Formula (II)



[0023] m is 1 and R<sup>20</sup> is selected from H, halo, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>haloalkoxy, deuterium, deuterated C<sub>1</sub>-C<sub>6</sub>alkyl,  $-CN$ ,  $-(CR^9)_nOR^4$ ,  $-C(O)R^4$ ,  $-(CR^9)_nC(=O)OR^4$ , R<sup>8</sup>,  $-(CR^9)_nR^8$ ,  $-(CR^9)_nO$ ,  $-(CR^9)_nR^4$ ,  $-(CR^9)_nO(CR^9)_nR^6$ ,  $-(CR^9)_nC(=O)R^4$ ,  $-C(=O)N(R^4)_2$ ,  $-(CR^9)_nOR^4$ ,  $-OR^4$  and  $-(CR^9)_nCN$ ;

[0024] or m is 4 and R<sup>20</sup> is deuterium;

[0025] R<sup>1</sup> is selected from C<sub>1</sub>-C<sub>6</sub>alkyl and halo;

[0026] each R<sup>11</sup> is independently selected from H, halo and C<sub>1</sub>-C<sub>6</sub>alkyl;

[0027] L<sub>1</sub> is a bond,  $-NH-$  or  $-C(O)NH-$ ;

[0028] R<sup>2</sup> is selected from C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl,  $-(CR^9)_nOR^4$ ,  $-(CR^9)_nR^6$ ,  $-(CR^9)_nS(=O)_2NR^4$ ,  $-(CR^9)_nCN$ ,  $-(CR^9)_nC(=O)R^4$ ,  $-(CR^9)_nOC(=O)R^4$ ,  $-(CR^9)_nC(=O)OR^4$ ,  $-(CR^9)_nC(=O)NR^4$ ,  $-(CR^9)_nOC(=O)NR^4$ ,  $(CR^9)_nOR^4$ ,  $-(CR^9)_nO(CR^9)_nOR^4$ ,  $-(CR^9)_nO(CR^9)_nR^6$ ,  $-(CR^9)_nO(CR^9)_nO(CR^9)_nR^6$ ,  $-(CR^9)_nOCR^9R^6$ ,  $-(CR^9)_nCR^9R^6$ ,  $-(CR^9)_nCR^5R^6R^6$ ,  $-(CR^9)_nCR^9R^5$ ,  $-(CR^9)_nR^6NR^4$ ,  $-(CR^9)_nNR^4$ ,  $-(CR^9)_nOR^4$ ,  $-(CR^9)_nR^6$ ,  $-(CR^9)_nNR^4(CR^9)_nR^4$ ,  $-(CR^9)_nNR^4C(=O)R^4$ ,  $-(CR^9)_nNR^4C(=O)OR^4$ ,  $-(CR^9)_nNR^4C(=O)NR^4$ ,  $-(CR^9)_nNR^4C(=O)R^6$ ,  $-(CR^9)_nNR^4S(=O)_2R^4$ ,  $-(CR^9)_nNR^4C(=O)O(CR^9)_nOR^4$ ,  $-(CR^9)_nNR^4C(=O)(CR^9)_nOR^4$ ,  $-(CR^9)_nNR^4S(=O)_2R^4$ ,  $-(CR^9)_nNR^5C(=O)R^6$ ,  $-(CR^9)_nNR^4C(=O)(CR^9)_nR^6$ ,  $-(CR^9)_nNR^4C(=O)O(CR^9)_nR^{11}$ ,  $-(CR^9)_nNR^4C(=O)(CR^9)_nO(CR^9)_nR^6$ , and  $-(CR^9)_nNR^4C(=O)O(CR^9)_nR^6$ ;

[0029] each R<sup>4</sup> is independently selected from H and C<sub>1</sub>-C<sub>6</sub>alkyl;

[0030] each R<sup>5</sup> is independently selected from  $-NHC(O)OR^4$ ,  $-OR^4$  and  $-(CR^9)_nOR^4$ ;

[0031] each R<sup>6</sup> is a C<sub>1</sub>-C<sub>6</sub>haloalkyl;

[0032] each R<sup>9</sup> is independently selected from H and C<sub>1</sub>-C<sub>6</sub>alkyl;

[0033] R<sup>8</sup> is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, O or S, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a sub-

stituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

**[0034]** wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl and substituted 4-6 membered heterocycloalkyl of R<sup>8</sup> are substituted with 1-3 substituents independently selected from C<sub>1</sub>-C<sub>6</sub>alkyl, halo,  $-(C(R^9)_2)_nOR^4$ ,  $-C(O)NR^4_2$ ,  $-NR^4_2$ ,  $-R^{10}$ ,  $-(C(R^9)_2)_nR^{10}$ ,  $-OR^4$ ,  $(C(R^9)_2)_nC(O)OR^4$  and  $-S(O)_2R^4$ ;

**[0035]** R<sup>10</sup> is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, and a substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl,

**[0036]** wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl and substituted 4-6 membered heterocycloalkyl of R<sup>10</sup> are substituted with 1-3 substituents independently selected from C<sub>1</sub>-C<sub>6</sub>alkyl, and  $-(C(R^9)_2)_nOR^4$ ;

**[0037]** t is 1, 2 or 3, and

**[0038]** each n is independently selected from 1, 2, 3 and 4.

**[0039]** In certain embodiments of compounds of Formula (I) or Formula (II),

**[0040]** m is 1 and R<sup>20</sup> is selected from H,  $-F$ , C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>haloalkoxy, deuterium, deuterated C<sub>1</sub>-C<sub>6</sub>alkyl,  $-CN$ ,  $-(CR^9_2)_nOR^4$ ,  $-C(O)R^4$ ,  $-(CR^9_2)_nC(=O)OR^4$ , R<sup>8</sup>,  $-(CR^9_2)_nR^8$ ,  $-(CR^9_2)_nO)R^4$ ,  $-(CR^9_2)_nO(CR^9_2)_nR^8$ ,  $-(CR^9_2)_nC(=O)R^4$ ,  $-C(=O)N(R^4)_2$ ,  $-(CR^9_2)_nOR^4$ ,  $-OR^4$  and  $-(CR^9_2)_nCN$ ;

**[0041]** or m is 4 and R<sup>20</sup> is deuterium;

**[0042]** R<sup>1</sup> is selected from C<sub>1</sub>-C<sub>6</sub>alkyl and halo;

**[0043]** each R<sup>11</sup> is independently selected from H, halo and C<sub>1</sub>-C<sub>6</sub>alkyl;

**[0044]** L<sub>1</sub> is a bond,  $-NH-$  or  $-C(O)NH-$ ;

**[0045]** R<sup>2</sup> is selected from C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl,  $-(CR^9_2)_nOR^4$ ,  $-(CR^9_2)_nR^6$ ,  $-(CR^9_2)_nS(=O)_2NR^4_2$ ,  $-(CR^9_2)_nCN$ ,  $-(CR^9_2)_nC(=O)R^4$ ,  $-(CR^9_2)_nOC(=O)R^4$ ,  $-(CR^9_2)_nC(=O)OR^4$ ,  $-(CR^9_2)_nC(=O)NR^4_2$ ,  $-(CR^9_2)_nOC(=O)ONR^4$ ,  $(CR^9_2)_nOR^4$ ,  $-(CR^9_2)_nO(CR^9_2)_nOR^4$ ,  $-(CR^9_2)_nO(CR^9_2)_nR^6$ ,  $-(CR^9_2)_nO(CR^9_2)_nO(CR^9_2)_nR^6$ ,  $-(CR^9_2)_nOCR^9R^6$ ,  $-(CR^9_2)_nCR^9R^5R^6$ ,  $-(CR^9_2)_nCR^5R^6R^6$ ,  $-(CR^9_2)_nR^6$ ,  $-(CR^9_2)_nR^5$ ,  $-(CR^9_2)_nR^6NR^4_2$ ,  $-(CR^9_2)_nNR^4_2$ ,  $-NR^4(CR^9_2)_nOR^4$ ,  $-NR^4(CR^9_2)_nR^6$ ,  $-NR^4(CR^9_2)_nR^4$ ,  $-(CR^9_2)NR^4C(=O)R^4$ ,  $-(CR^9_2)_nNR^4C(=O)OR^4$ ,  $-(CR^9_2)NR^4C(=O)NR^4_2$ ,  $-(CR^9_2)NR^4C(=O)R^6$ ,  $-(CR^9_2)_nNR^4S(=O)_2R^4$ ,  $-(CR^9_2)_nNR^4C$

$(=O)O(CR^9_2)_nOR^4$ ,  $-(CR^9_2)_nNR^4C(=O)(CR^9_2)_nOR^4$ ,  $-CR^9R^5NR^4S(=O)_2R^4$ ,  $-(CR^9_2)_nNR^5C(=O)R^6$ ,  $-(CR^9_2)_nNR^4C(=O)(CR^9_2)_nR^6$ ,  $-(CR^9_2)_nNR^4C(=O)O(CR^9_2)_nR^{11}$ ,  $-(CR^9_2)_nNR^4C(=O)(CR^9_2)_nO(CR^9_2)_nR^6$ , and  $-(CR^9_2)_nNR^4C(=O)O(CR^9_2)_nR^6$ ;

**[0046]** each R<sup>4</sup> is independently selected from H and C<sub>1</sub>-C<sub>6</sub>alkyl;

**[0047]** each R<sup>5</sup> is independently selected from  $-NHC(O)OR^4$ ,  $-OR^4$  and  $-(CR^9_2)_nOR^4$ ;

**[0048]** each R<sup>6</sup> is a C<sub>1</sub>-C<sub>6</sub>haloalkyl;

**[0049]** each R<sup>9</sup> is independently selected from H and C<sub>1</sub>-C<sub>6</sub>alkyl;

**[0050]** R<sup>8</sup> is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

**[0051]** wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl and substituted 4-6 membered heterocycloalkyl of R<sup>8</sup> are substituted with 1-3 substituents independently selected from C<sub>1</sub>-C<sub>6</sub>alkyl, halo,  $-(C(R^9)_2)_nOR^4$ ,  $-C(O)NR^4_2$ ,  $-NR^4_2$ ,  $-R^{10}$ ,  $-(C(R^9)_2)_nR^{10}$ ,  $-OR^4$ ,  $-(C(R^9)_2)_nC(O)OR^4$  and  $-S(O)_2R^4$ ;

**[0052]** R<sup>10</sup> is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, and a substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl,

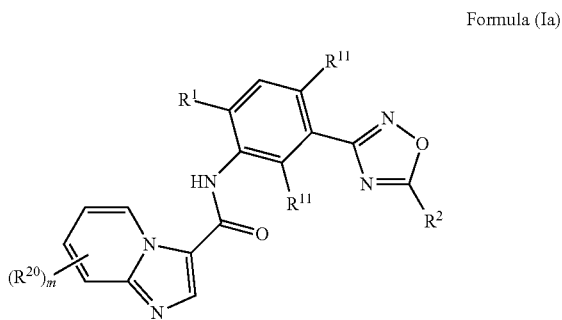
**[0053]** wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl and substituted 4-6 membered heterocycloalkyl of R<sup>10</sup> are substituted with 1-3 substituents independently selected from C<sub>1</sub>-C<sub>6</sub>alkyl, and  $-(C(R^9)_2)_nOR^4$ ;

**[0054]** t is 1, 2 or 3, and

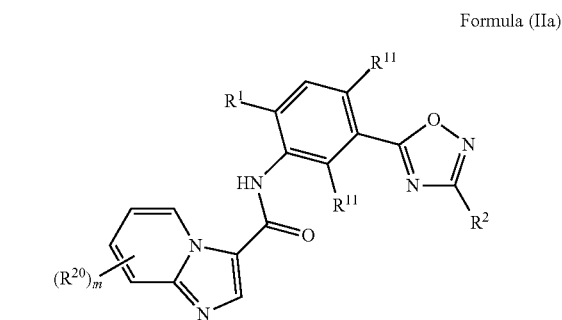
**[0055]** each n is independently selected from 1, 2, 3 and 4.

**[0056]** In certain embodiments of compounds of Formula (I) or Formula (II), and the pharmaceutically acceptable salts,

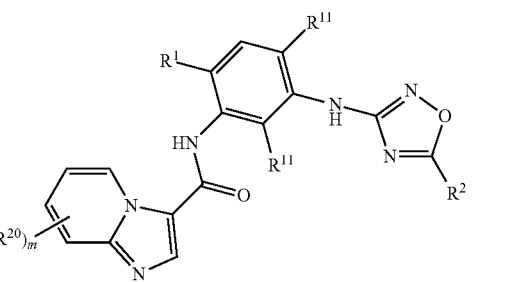
pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, the compound of Formula (I) or Formula (II) is a compound having a structure of Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf):



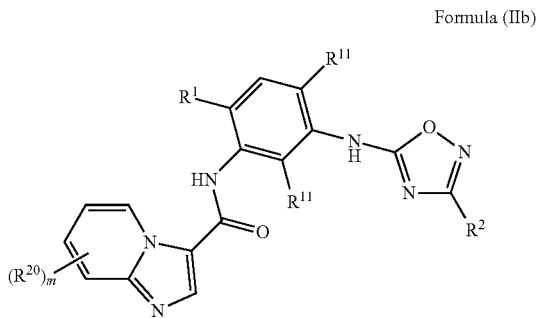
Formula (Ia)



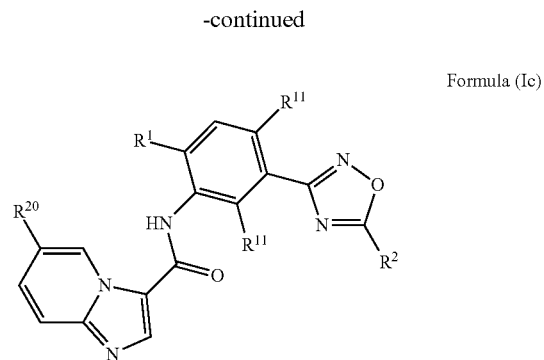
Formula (IIa)



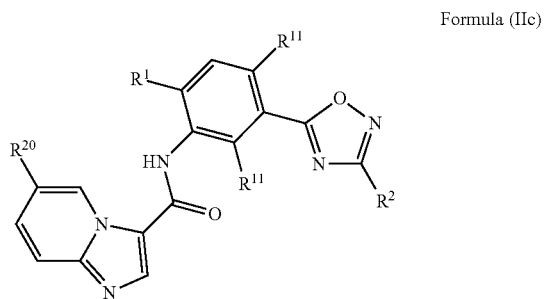
Formula (Ib)



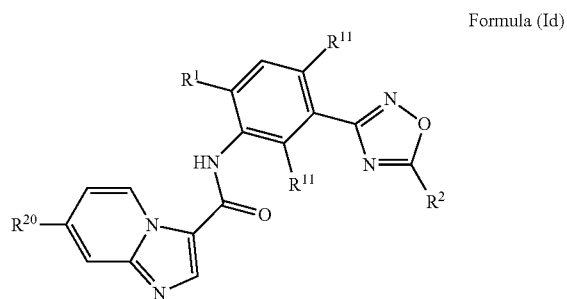
Formula (IIb)



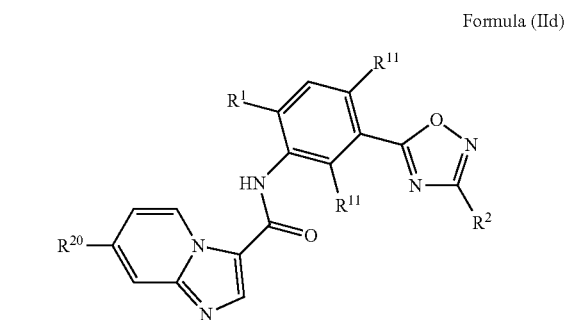
Formula (Ic)



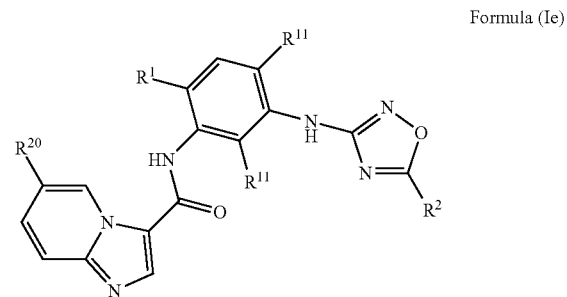
Formula (IIc)



Formula (Id)



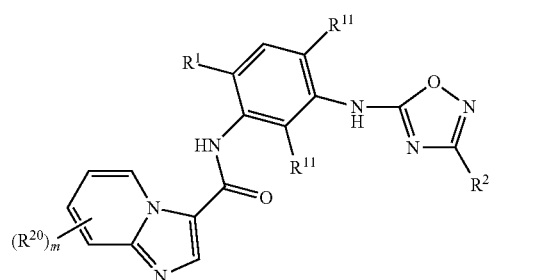
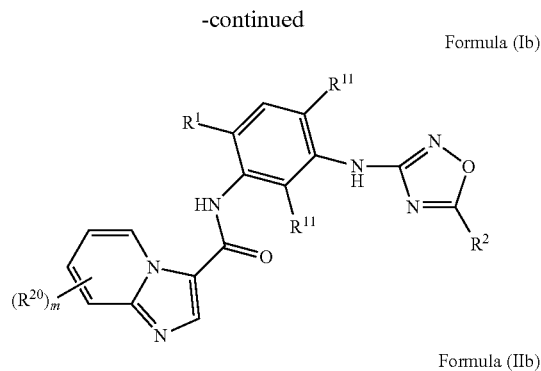
Formula (IId)



Formula (Ie)







wherein:

**[0089]**  $m$  is 1 and  $R^{20}$  is selected from H, halo,  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ haloalkyl,  $C_1$ - $C_6$ haloalkoxy, deuterium, deuterated  $C_1$ - $C_6$ alkyl,  $-\text{CN}$ ,  $-(\text{CR}^9)_2\text{OR}^4$ ,  $-\text{C}(\text{O})\text{R}^4$ ,  $-(\text{CR}^9)_2\text{C}(\text{O})\text{OR}^4$ ,  $R^8$ ,  $-(\text{CR}^9)_2\text{R}^8$ ,  $-(\text{CR}^9)_2\text{O}$ ,  $\text{R}^4$ ,  $-(\text{CR}^9)_2\text{O}(\text{CR}^9)_2\text{R}^6$ ,  $-(\text{CR}^9)_2\text{C}(\text{O})\text{R}^4$ ,  $-\text{C}(\text{O})\text{N}(\text{R}^4)_2$ ,  $-(\text{CR}^9)_2\text{OR}^4$ ,  $-\text{OR}^4$  and  $-(\text{CR}^9)_2\text{CN}$ ;

**[0090]**  $m$  is 4 and  $R^{20}$  is deuterium;

**[0091]**  $R^1$  is selected from  $C_1$ - $C_6$ alkyl and halo;

**[0092]** each  $R^{11}$  is independently selected from H, halo and  $C_1$ - $C_6$ alkyl;

**[0093]**  $R^2$  is selected from  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ haloalkyl,  $C_2$ - $C_8$ alkenyl,  $-(\text{CR}^9)_2\text{OR}^4$ ,  $-(\text{CR}^9)_2\text{R}^6$ ,  $-(\text{CR}^9)_2\text{S}(\text{O})_2\text{NR}^4$ ,  $-(\text{CR}^9)_2\text{CN}$ ,  $-(\text{CR}^9)_2\text{C}(\text{O})\text{R}^4$ ,  $-(\text{CR}^9)_2\text{OC}(\text{O})\text{R}^4$ ,  $-(\text{CR}^9)_2\text{C}(\text{O})\text{OR}^4$ ,  $-(\text{CR}^9)_2\text{C}(\text{O})\text{NR}^4$ ,  $-(\text{CR}^9)_2\text{OC}(\text{O})\text{ONR}^4$ ,  $(\text{CR}^9)_2\text{OR}^4$ ,  $-(\text{CR}^9)_2\text{O}(\text{CR}^9)_2\text{OR}^4$ ,  $-(\text{CR}^9)_2\text{O}(\text{CR}^9)_2\text{R}^6$ ,  $-(\text{CR}^9)_2\text{O}(\text{CR}^9)_2\text{O}(\text{CR}^9)_2\text{R}^6$ ,  $-(\text{CR}^9)_2\text{OCR}^9\text{R}^6\text{R}^6$ ,  $-(\text{CR}^9)_2\text{CR}^9\text{R}^6$ ,  $-(\text{CR}^9)_2\text{CR}^8\text{R}^6\text{R}^6$ ,  $-(\text{CR}^9)\text{R}^8\text{R}^6$ ,  $-(\text{CR}^9)\text{R}^6\text{NR}^4$ ,  $-(\text{CR}^9)_2\text{NR}^4$ ,  $-\text{NR}^4(\text{CR}^9)_2\text{OR}^4$ ,  $-\text{NR}^4(\text{CR}^9)_2\text{R}^6$ ,  $-\text{NR}^4(\text{CR}^9)_2\text{R}^4$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{R}^4$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{OR}^4$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{NR}^4$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{O}(\text{CR}^9)_2\text{R}^6$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{S}(\text{O})_2\text{R}^4$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{O}(\text{CR}^9)_2\text{OR}^4$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{O}(\text{CR}^9)_2\text{R}^6$ ,  $-(\text{CR}^9)_2\text{NR}^8\text{C}(\text{O})\text{R}^6$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{O}(\text{CR}^9)_2\text{R}^6$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{O}(\text{CR}^9)_2\text{R}^6$ , and  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{O}(\text{CR}^9)_2\text{R}^6$ ;

**[0094]** each  $R^4$  is independently selected from H and  $C_1$ - $C_6$ alkyl;

**[0095]** each  $R^5$  is independently selected from  $-\text{NHC}(\text{O})\text{OR}^4$ ,  $-\text{OR}^4$  and  $-(\text{CR}^9)_2\text{OR}^4$ ;

**[0096]** each  $R^6$  is a  $C_1$ - $C_6$ haloalkyl;

**[0097]** each  $R^9$  is independently selected from H and  $C_1$ - $C_6$ alkyl;

**[0098]**  $R^8$  is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted  $C_3$ - $C_8$ cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted  $C_3$ - $C_8$ cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

**[0099]** wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted  $C_3$ - $C_8$ cycloalkyl and substituted 4-6 membered heterocycloalkyl of  $R^8$  are substituted with 1-3 substituents independently selected from  $C_1$ - $C_6$ alkyl, halo,  $-(\text{C}(\text{R}^9)_2)_n\text{OR}^4$ ,  $-\text{C}(\text{O})\text{NR}^4$ ,  $-\text{NR}^4$ ,  $-\text{R}^{10}$ ,  $-(\text{C}(\text{R}^9)_2)_n\text{R}^{10}$ ,  $-\text{OR}^4$ ,  $-(\text{C}(\text{R}^9)_2)_n\text{C}(\text{O})\text{OR}^4$  and  $-\text{S}(\text{O})_2\text{R}^4$ ;

**[0100]**  $R^{10}$  is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted  $C_3$ - $C_8$ cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, and a substituted  $C_3$ - $C_8$ cycloalkyl,

**[0101]** wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted  $C_3$ - $C_8$ cycloalkyl and substituted 4-6 membered heterocycloalkyl of  $R^{10}$  are substituted with 1-3 substituents independently selected from  $C_1$ - $C_6$ alkyl, and  $-(\text{C}(\text{R}^9)_2)_n\text{OR}^4$ ;

**[0102]**  $t$  is 1, 2 or 3, and

**[0103]** each  $n$  is independently selected from 1, 2, 3 and 4.

**[0104]** In certain embodiments of compounds of Formula (Ia), Formula (IIa), Formula (Ib) or Formula (IIb),

**[0105]**  $m$  is 1 and  $R^{20}$  is selected from H,  $-\text{F}$ ,  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ haloalkyl,  $C_1$ - $C_6$ haloalkoxy, deuterium, deuterated  $C_1$ - $C_6$ alkyl,  $-\text{CN}$ ,  $-(\text{CR}^9)_2\text{OR}^4$ ,  $-\text{C}(\text{O})\text{R}^4$ ,  $-(\text{CR}^9)_2\text{C}(\text{O})\text{OR}^4$ ,  $R^8$ ,  $-(\text{CR}^9)_2\text{R}^8$ ,  $-(\text{CR}^9)_2\text{O}$ ,  $\text{R}^4$ ,  $-(\text{CR}^9)_2\text{O}(\text{CR}^9)_2\text{R}^6$ ,  $-(\text{CR}^9)_2\text{C}(\text{O})\text{R}^4$ ,  $-\text{C}(\text{O})\text{N}(\text{R}^4)_2$ ,  $-(\text{CR}^9)_2\text{OR}^4$ ,  $-\text{OR}^4$ ,  $-(\text{CR}^9)_2\text{CN}$ ;

**[0106]**  $m$  is 4 and  $R^{20}$  is deuterium;

**[0107]**  $R^1$  is selected from  $C_1$ - $C_6$ alkyl and halo;

**[0108]** each  $R^{11}$  is independently selected from H, halo and  $C_1$ - $C_6$ alkyl;





Formula (Iie), Formula (Iif) or Formula (Iif), each R<sup>5</sup> is independently selected from, —OW and —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>.

**[0128]** In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), each R<sup>5</sup> is independently selected from OH and —CH<sub>2</sub>OH.

**[0129]** In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), each R<sup>6</sup> is independently selected from —CH<sub>2</sub>F, —CHF<sub>2</sub>, —CH<sub>2</sub>CHF<sub>2</sub>, —CH<sub>2</sub>CF<sub>3</sub> and —CF<sub>3</sub>.

**[0130]** In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), each R<sup>9</sup> is independently selected from H, methyl and ethyl.

**[0131]** In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), R<sup>2</sup> is selected from —CH<sub>3</sub>, —CH(CH<sub>3</sub>)<sub>2</sub>, —CH<sub>2</sub>OCH<sub>3</sub>, —CH<sub>2</sub>OH, —C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>OH, —CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>OH, —CH<sub>2</sub>CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>OH, —CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub>, CH(F)CF<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub>, —CH<sub>2</sub>CH=C(CH<sub>3</sub>)<sub>2</sub>, —C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>OH, —CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)OH, —CH<sub>2</sub>CH<sub>2</sub>CN, —CHF<sub>2</sub>, —CH<sub>2</sub>F, —CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, —CH(CH<sub>3</sub>)OCH<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>CH(OH)CF<sub>3</sub>, —CH<sub>2</sub>C(CH<sub>3</sub>)OHCf<sub>3</sub>, —CH<sub>2</sub>C(CF<sub>3</sub>)<sub>2</sub>OH, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, —CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CF<sub>3</sub>, —CH<sub>2</sub>CH(OH)CF<sub>3</sub>, —CH(OH)CF<sub>3</sub>, —CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, —CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OH, —CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH(CH<sub>3</sub>)<sub>2</sub>, —CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OC(CH<sub>3</sub>)<sub>3</sub>, —CH<sub>2</sub>OCH<sub>2</sub>CF<sub>3</sub>, —CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CF<sub>3</sub>, —NHCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>C(CH<sub>3</sub>)OHCf<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>S(=O)<sub>2</sub>NH<sub>2</sub>, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>S(=O)<sub>2</sub>NH<sub>2</sub>, —CH(CH<sub>3</sub>)OH, —CH<sub>2</sub>CH<sub>2</sub>NHS(=O)<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NHS(=O)<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>NHS(=O)<sub>2</sub>CH<sub>3</sub>, —C(CH<sub>2</sub>OH)<sub>2</sub>NHS(=O)<sub>2</sub>CH<sub>3</sub>, —CH(CH<sub>3</sub>)NHC(=O)OCH<sub>3</sub>, —CH(CH<sub>3</sub>)NHS(=O)<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>NHS(=O)<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)S(=O)<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>NHS(=O)<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, —CH<sub>2</sub>CH<sub>2</sub>NHC(=O)OCH<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>NHC(=O)OCH<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>NHC(=O)OC(CH<sub>3</sub>)<sub>3</sub>, —CH(CH<sub>3</sub>)NH<sub>2</sub>, —CH<sub>2</sub>C(=O)NHCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>NHC(=O)OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, —CH<sub>2</sub>NHC(=O)C(CH<sub>3</sub>)<sub>2</sub>OH, —CH<sub>2</sub>N(CH<sub>3</sub>)S(=O)<sub>2</sub>CH<sub>3</sub>, —C(CH<sub>3</sub>)<sub>2</sub>NHC(=O)OC(CH<sub>3</sub>)<sub>3</sub>, —CH<sub>2</sub>CH(CH<sub>3</sub>)NHC(=O)C(CH<sub>3</sub>)<sub>3</sub>, —CH<sub>2</sub>NHCH<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NHC(=O)OC(CH<sub>3</sub>)<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, —CH<sub>2</sub>CH<sub>2</sub>C(=O)NH<sub>2</sub>, —C(CH<sub>3</sub>)<sub>2</sub>NHS(=O)<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>C(=O)CH<sub>3</sub>, —CH<sub>2</sub>NHC(=O)OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, —CH<sub>2</sub>NHC(=O)CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CF<sub>3</sub>, —NHCH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>OH, —CH<sub>2</sub>CH<sub>2</sub>C(=O)OCH(CH<sub>3</sub>)<sub>2</sub>, —CH<sub>2</sub>CH(CH<sub>3</sub>)NHS(=O)<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>CH(CH<sub>3</sub>)NHC(=O)OCH<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>C(=O)NHCH<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>NHC(=O)CH<sub>3</sub>, —CH<sub>2</sub>NHC(=O)OC(CH<sub>3</sub>)<sub>3</sub>, —CH<sub>2</sub>NHC(=O)CH<sub>2</sub>OCH<sub>3</sub>, —CH<sub>2</sub>NHC(=O)CH(CH<sub>3</sub>)OCH<sub>3</sub>, —CH(CH<sub>3</sub>)NHC(=O)OC(CH<sub>3</sub>)<sub>3</sub>, —CH<sub>2</sub>NHC(=O)OCH<sub>3</sub>, —CH<sub>2</sub>N(CH<sub>3</sub>)C(=O)OC(CH<sub>3</sub>)<sub>3</sub>, —CH<sub>2</sub>N

(CH<sub>2</sub>CH<sub>3</sub>)C(=O)OC(CH<sub>3</sub>)<sub>3</sub>, —CH(CH<sub>2</sub>CF<sub>3</sub>)N(CH<sub>3</sub>)<sub>2</sub>, —CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)C(=O)OCH<sub>3</sub>, —CH<sub>2</sub>NHC(=O)CF<sub>3</sub>, —CH<sub>2</sub>OCH(CH<sub>3</sub>)CF<sub>3</sub>, —CH<sub>2</sub>OCH(CH<sub>2</sub>F)<sub>2</sub>, —CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>)C(=O)CF<sub>3</sub>, —CH<sub>2</sub>NHC(=O)OCH<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>NHC(=O)OCH(CH<sub>3</sub>)<sub>2</sub>, —CH<sub>2</sub>NHC(=O)CH<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub>, —CH<sub>2</sub>NHC(=O)CH<sub>2</sub>CF<sub>3</sub>, —CH<sub>2</sub>NHC(=O)OCH<sub>2</sub>CHF<sub>2</sub>, —CH<sub>2</sub>CH<sub>2</sub>C(=O)N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, —CH<sub>2</sub>CH<sub>2</sub>C(=O)CH<sub>3</sub>, —CH<sub>2</sub>C(=O)OCH<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>NHC(=O)OCH<sub>2</sub>CH<sub>2</sub>F, —CH<sub>2</sub>C(=O)OC(CH<sub>3</sub>)<sub>3</sub>, —N(CH<sub>3</sub>)CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>OH, —NHCH<sub>2</sub>CH<sub>2</sub>F, and —NHCH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>.

**[0132]** In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), R<sup>2</sup> is —C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>OH or —CH<sub>2</sub>CH<sub>2</sub>C(CH<sub>3</sub>)OHCf<sub>3</sub>.

**[0133]** In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), m is 1 and R<sup>20</sup> is selected from H, halo, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, deuterated C<sub>1</sub>-C<sub>6</sub>alkyl, —CN, —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —R<sup>8</sup>, —(CR<sup>9</sup>)<sub>n</sub>R<sup>8</sup>, —(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>R<sup>8</sup>, —(CR<sup>9</sup>)<sub>n</sub>C(=O)R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup> and —OR<sup>4</sup>.

**[0134]** In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), m is 1 and R<sup>20</sup> is selected from H, —F, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, deuterated C<sub>1</sub>-C<sub>6</sub>alkyl, —CN, —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —R<sup>8</sup>, —(CR<sup>9</sup>)<sub>n</sub>R<sup>8</sup>, —(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>R<sup>8</sup>, —(CR<sup>9</sup>)<sub>n</sub>C(=O)R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup> and —OR<sup>4</sup>.

**[0135]** In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), m is 1 and R<sup>20</sup> is selected from H, —F, —CH<sub>3</sub>, —CF<sub>3</sub>, —CD<sub>3</sub>, —CN, —OCHF<sub>2</sub>, —CH<sub>2</sub>CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>OH, —CH<sub>2</sub>OCH<sub>2</sub>CF<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>C(=O)CH<sub>3</sub>, —CH<sub>2</sub>OCH<sub>3</sub> and —OCH<sub>3</sub>.

**[0136]** In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), m is 1 and R<sup>20</sup> is —CH<sub>3</sub>.

**[0137]** In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), m is 1 and R<sup>20</sup> is H.

**[0138]** In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), R<sup>8</sup> is selected from phenyl, morpholinyl, cyclopropyl, pyridinyl, pyridine-3-yl, pyridine-4-yl, pyrazolyl, pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, pyrrolyl, triazolyl, 1H-1,2,3-triazol-4-yl, 4H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, thiazolyl, thiazol-4-

yl, thiazol-5-yl, isoxazolyl and isoxazol-4-yl, each of which is unsubstituted or each of which is substituted with 1-3 substituents independently selected from halo, C<sub>1</sub>-C<sub>6</sub>alkyl, —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —C(O)NR<sup>4</sup><sub>2</sub> and —OR<sup>4</sup>, or R<sup>8</sup> is selected from a oxazolidin-2-one and a pyrrolidin-2-one.

**[0139]** In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIIf), R<sup>8</sup> is selected from phenyl, morpholinyl, cyclopropyl, pyridinyl, pyridine-3-yl, pyridine-4-yl, pyrazolyl, pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, pyrrolyl, triazolyl, 1H-1,2,3-triazol-4-yl, 4H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, thiazolyl, thiazol-4-yl, thiazol-5-yl, isoxazolyl and isoxazol-4-yl, each of which is unsubstituted or each of which is substituted with 1-3 substituents independently selected from F, —CH<sub>3</sub>, —C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>OH, —CH<sub>2</sub>OCH<sub>3</sub>, —C(O)NHCH<sub>3</sub>, —NH<sub>2</sub> and —OCH<sub>3</sub>.

**[0140]** In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib) or Formula (IIb), m is 4 and R<sup>20</sup> is deuterium.

**[0141]** Certain embodiments of the compounds of Formula (I) or Formula (II) are selected from: N-{5-[5-(2-cyanoethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; tert-butyl N-{2-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]ethyl}carbamate; N-{5-[5-(3-methoxypropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[2-(diethylcarbamoyl)ethyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{2-methyl-5-[5-(3-oxobutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; tert-butyl N-{[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate; ethyl 2-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]acetate; N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-hydroxybutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(2-ethoxyethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(ethoxymethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; tert-butyl N-[(1S)-1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]ethyl]carbamate; N-(5-{5-[(1R)-1-methoxyethyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{2-methyl-5-[5-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(2-methyl-5-{5-[3,3,3-trifluoro-2-hydroxy-2-(trifluoromethyl)propyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(1,3-dihydroxy-2-methanesulfonamidopropan-2-yl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(1R)-1-methanesulfonamidoethyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; tert-butyl N-{[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}-N-methylcarbamate; N-{5-[5-

(ethanesulfonamidomethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; tert-butyl N-ethyl-N-{[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate; N-(5-{5-[(N-ethylmethanesulfonamido)methyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; methyl N-ethyl-N-{[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate; N-(2-methyl-5-{5-[(2,2,2-trifluoroacetamido)methyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{2-methyl-5-[5-(propane-2-sulfonamidomethyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(2-methoxyethoxy)methyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; tert-butyl 2-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]acetate; N-(2-methyl-5-{5-[2-(2,2,2-trifluoroethoxy)ethyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; ethyl N-{[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate; propan-2-yl N-{[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate; N-(2-methyl-5-{5-[(2R)-3,3,3-trifluoro-2-hydroxypropyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(2-ethoxyethoxy)methyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-{[2-(propan-2-yloxy)ethoxy]methyl}-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-[5-(5-{[2-(tert-butoxy)ethoxy]methyl}-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-(2-methyl-5-{5-[(3,3,3-trifluoropropanamido)methyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 6-fluoro-N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; 6-fluoro-N-(5-{5-[(2-methoxyethoxy)methyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; ethyl N-{[3-(3-{6-fluoroimidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate; N-(2-methyl-5-{5-[(2,2,2-trifluoroethoxy)methyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 2,2-difluoroethyl N-{[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate; methyl N-([3-[4-methyl-3-(7-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-4-yl]imidazo[1,2-a]pyridine-3-amido]phenyl]-1,2,4-oxadiazol-5-yl]methyl)carbamate; N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(1-methyl-1H-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-(1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide; 6-(1-methyl-1H-pyrazol-4-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; 6-[1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl]-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{[5-(1-hydroxy-2-methylpropan-2-yl)-1,2,4-oxadiazol-3-yl]amino}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-(1,3-thiazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide; 6-(2,4-dimethyl-1,3-thiazol-5-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; 6-(3,5-dimethyl-1,

2-oxazol-4-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-methylimidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-4-yl}imidazo[1,2-a]pyridine-3-carboxamide; 5,6,7,8-tetradeutero-N-{2-methyl-5-[5-(3-methylbut-2-en-1-yl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; 5,6,7,8-tetradeutero-N-(5-{5-[(2-methoxyethoxy)methyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; 5,6,7,8-tetradeutero-N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; propan-2-yl 3-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]propanoate; N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-methoxyimidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-methylimidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(2-methoxyethoxy)methyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)-6-methylimidazo[1,2-a]pyridine-3-carboxamide; N-{2-methyl-5-[5-(pentan-2-yl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(morpholin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(2-oxo-1,2,4-oxazolidin-3-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(2-oxopyrrolidin-1-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide; 7-cyclopropyl-N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; 7-fluoro-N-(5-{5-[(2-hydroxy-2-methylpropyl)(methylamino)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{2-methyl-5-[5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; 7-methyl-N-{2-methyl-5-[5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(2-fluoroethyl)amino]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide; 7-methyl-N-(2-methyl-5-[5-(2-methylpropyl)amino]-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 7-fluoro-N-{2-methyl-5-[5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; 6-fluoro-N-{2-methyl-5-[5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; 6-methyl-N-{2-methyl-5-[5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; 5,6,7,8-tetradeutero-N-{2-methyl-5-[5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{2-methyl-5-[5-(3,3,3-trifluoropropyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; 7-methyl-N-(2-methyl-5-[5-(3S)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-

carboxamide; 7-methyl-N-(2-methyl-5-[5-[(3R)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 7-methyl-N-(2-methyl-5-[5-[(2,2,2-trifluoroethoxy)methyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 7-methyl-N-(2-methyl-5-[5-[(2,2,2-trifluoroethoxy)methyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 6-methyl-N-(2-methyl-5-[5-[(2,2,2-trifluoroethoxy)methyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(2-methyl-5-[5-(4,4,4-trifluorobutyl)-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-(2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-(2-methylpyridin-3-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-(3-methylpyridin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide; 6-methyl-N-(2-methyl-5-[5-(3S)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 6-fluoro-N-(2-methyl-5-[5-(3S)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 7-fluoro-N-(2-methyl-5-[5-(3S)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 6-methyl-N-(2-methyl-5-[5-[(3R)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 6-fluoro-N-(2-methyl-5-[5-(3R)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 7-fluoro-N-(2-methyl-5-[5-(3R)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 6-(2,4-dimethyl-1,3-thiazol-5-yl)-N-(2-methyl-5-[5-[(2,2,2-trifluoroethoxy)methyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 6-(2-fluoropyridin-3-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-methyl-5-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)pyridine-2-carboxamide; N-(5-{5-[(2,2-difluoroethoxy)methyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[(1,3-difluoropropan-2-yl)oxy]methyl}-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-[(1,1,1-trifluoropropan-2-yl)oxy]methyl)-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 6-(4-methyl-1,3-thiazol-5-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; 7-methyl-N-(2-methyl-5-[5-(4,4,4-trifluoro-3-hydroxybutyl)-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide; 6-(1-methyl-1H-pyrazol-2-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; 6-(4-methoxypyridin-3-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-

carboxamide; 6-(2-aminopyridin-4-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; tert-butyl 2-[3,5-dimethyl-4-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-1H-pyrazol-1-yl]acetate; 2-[3,5-dimethyl-4-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-1H-pyrazol-1-yl]acetic acid; 6-[5-(1-hydroxyethyl)-4-methyl-1,3-thiazol-2-yl]-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; 6-(4,5-dimethyl-1,3-thiazol-2-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; 6-(1-[(2-hydroxyethyl)carbamoyl]methyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; 6-[3,5-dimethyl-1-((2-(morpholin-4-yl)ethyl)carbamoyl)methyl)-1H-pyrazol-4-yl]-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; 3-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3,6-dicarboxamide; 6-carbamothioyl-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-(2-hydroxyethyl)-4-methyl-2-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-1,3-thiazole-5-carboxamide; 4-methyl-2-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-N-[2-(4-methylpiperazin-1-yl)ethyl]-1,3-thiazole-5-carboxamide; 4-methyl-2-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-N-[3-(4-methylpiperazin-1-yl)propyl]-1,3-thiazole-5-carboxamide; 4-methyl-2-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-N-[2-(morpholin-4-yl)ethyl]-1,3-thiazole-5-carboxamide; 8-amino-N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; 4-methyl-5-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-1,3-thiazole-2-carboxylic acid; 4-methyl-5-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-N-[2-(4-methylpiperazin-1-yl)ethyl]-1,3-thiazole-2-carboxamide; 2-methyl-4-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]butan-2-yl-2-aminoacetate; methoxy{[(2R)-1,1,1-trifluoro-2-methyl-4-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]butan-2-yl]oxy}phosphonic acid; (2R)-1,1,1-trifluoro-2-methyl-4-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]butan-2-yl (2R)-2-amino-3-methylbutanoate; (2S)-1,1,1-trifluoro-2-methyl-4-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]butan-2-yl (2R)-2-amino-3-methylbutanoate; 7-methyl-N-{2-methyl-5-[5-(4,4,4-trifluoro-3-hydroxybutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; 7-methyl-N-(2-methyl-5-{5-[3,3,3-trifluoro-2-hydroxy-2-(trifluoromethyl)propyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 6-[1-(2-hydroxyethyl)-3,5-dimethyl-1H-pyrazol-4-yl]-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; 6-(5-acetyl-4-methyl-1,3-thiazol-2-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; 6-(3-

methyl-1H-pyrazol-4-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N,4-dimethyl-2-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-1,3-thiazole-5-carboxamide; 4-methyl-2-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3H)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-1,3-thiazole-5-carboxamide; 6-{3,5-dimethyl-1-[(methylcarbamoyl)methyl]-1H-pyrazol-4-yl}-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; ethyl 4-methyl-5-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-1,3-thiazole-2-carboxylate; 4-methyl-5-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-N-[2-(morpholin-4-yl)ethyl]-1,3-thiazole-2-carboxamide; N-(2-hydroxyethyl)-4-methyl-5-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-1,3-thiazole-2-carboxamide; 4-methyl-5-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-1,3-thiazole-2-carboxamide; 6-[2-(hydroxymethyl)-4-methyl-1,3-thiazol-5-yl]-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-(2-methyl-5-{5-[1-(2,2,2-trifluoroethoxy)ethyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide; dimethyl (2R)-1,1,1-trifluoro-2-methyl-4-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]butan-2-yl phosphate; {[2(R)-1,1,1-trifluoro-2-methyl-4-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]butan-2-yl]oxy}phosphonic acid; dimethyl (2S)-1,1,1-trifluoro-2-methyl-4-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]butan-2-yl phosphate; {[2(S)-1,1,1-trifluoro-2-methyl-4-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]butan-2-yl]oxy}phosphonic acid, and 1,1,1-trifluoro-2-methyl-4-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]butan-2-yl (2S)-2-aminopropanoate.

**[0142]** Certain preferred embodiments of the compounds of Formula (I) are selected from: N-(5-{5-(1-hydroxy-2-methylpropan-2-yl)-1,2,4-oxadiazol-3-yl}amino)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; 7-methyl-N-(2-methyl-5-{5-(3S)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide, and 7-methyl-N-(2-methyl-5-{5-[(3R)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide.

**[0143]** Other embodiments of the compounds of Formula (I) or Formula (II) are selected from: N-{2-methyl-5-[3-(propan-2-yl)-1,2,4-oxadiazol-5-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[3-(methoxyethyl)-1,2,4-oxadiazol-5-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(1-hydroxy-2-methylpropan-2-yl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{2-methyl-5-[5-(3-sulfamoylpropyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; tert-butyl N-{3-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]propyl}carbamate; N-{5-[5-(3-aminopropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(2-acetamidoethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(2-methanesulfonamidoethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-methanesulfonamidopropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{2-methyl-5-[5-(2-sulfamoyl)ethyl]-1,2,4-oxadiazol-3-yl}phenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(2-carbamoyl)ethyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[2-(ethylcarbamoyl)ethyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; methyl N-{2-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]ethyl}carbamate; N-{5-[5-(3-hydroxybutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; methyl N-{2-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]ethyl}carbamate; 2-methoxyethyl N-{2-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]ethyl}carbamate; N-{5-[5-(hydroxymethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[1(S)-1-aminoethyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; tert-butyl N-[(1R)-1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]ethyl}carbamate; N-(5-{5-[1(R)-1-aminoethyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; methyl N-{3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl}methyl}carbamate; N-{5-[5-(methanesulfonamidomethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(methoxymethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; [3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl N-(2-methoxyethyl)carbamate; N-(5-{5-(2-methoxyacetamido)methyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-[5-(5-{[(2R)-2-methoxypropanamido]methyl}-1,2,4-oxadiazol-3-yl)-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(2-hydroxy-2-methylpropanamido)methyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; methyl N-[(1S)-1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]ethyl}carbamate; N-(5-{5-[(1S)-1-methanesulfonamidoethyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; methyl N-[(1R)-1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]ethyl}carbamate; N-{5-[5-(2-hydroxy-2-methylpropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{2-fluoro-5-[5-(3-methoxypropyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(1S)-1-acetamidoethyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(acetamidomethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; tert-butyl N-[(2R)-1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]propan-2-yl]carbamate; tert-butyl N-{2-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]propan-2-yl}carbamate; N-(2-methyl-5-{5-[(N-

methylmethanesulfonamido)methyl]-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(ethylamino)methyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; 2-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]acetic acid; N-{5-[5-(2-methanesulfonamidopropan-2-yl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; methyl N-{2-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]propan-2-yl}carbamate; N-(5-{5-[(2R)-2-methanesulfonamidopropyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; methyl N-[(2R)-1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]propan-2-yl]carbamate; N-[2-methyl-5-(5-{[2,2,2-trifluoro-N-(3-methoxypropyl)acetamido]methyl}-1,2,4-oxadiazol-3-yl)phenyl}imidazo[1,2-a]pyridine-3-carboxamide; tert-butyl N-[[3-(4-fluoro-3-{imidazo[1,2-a]pyridine-3-amido]phenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate; N-(2-fluoro-5-{5-[3,3,3-trifluoro-2-hydroxy-2-(trifluoromethyl)propyl]-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(2-methyl-5-{5-[(4,4,4-trifluorobutanamido)methyl]-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(4-fluoro-5-{5-(2-methoxyethoxy)methyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; tert-butyl N-[[3-(2-fluoro-5-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate; 2-fluoroethyl N-[[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate; methyl N-[[3-(3-{7-cyanoimidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate; methyl N-[[3-(3-{7-fluoroimidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate; N-{5-[5-(difluoromethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(fluoromethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{2-methyl-5-[5-(2,2,2-trifluoro-1-hydroxyethyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(2-hydroxyethoxy)methyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-[5-(5-[[dimethylcarbamoyl]amino]methyl]-1,2,4-oxadiazol-3-yl)-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; 2-methoxyethyl N-[[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate; N-[2-methyl-5-(5-{[3-(2,2,2-trifluoroethoxy)propanamido]methyl}-1,2,4-oxadiazol-3-yl)phenyl}imidazo[1,2-a]pyridine-3-carboxamide; methyl N-[[3-(3-{6-fluoroimidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate; methyl N-[[3-(3-{6-cyanoimidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate; 7-fluoro-N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; methyl N-[(3-{4-methyl-3-[7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-amido]phenyl]-1,2,4-oxadiazol-5-yl]methyl}carbamate; N-(5-{5-[1-(dimethylamino)-3,3,3-trifluoropropyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; [3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl acetate; N-{5-[5-(2-hydroxypropan-2-yl)-1,2,4-oxadiazol-3-

yl]-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-(2-methyl-5-{[5-(propan-2-yl)-1,2,4-oxadiazol-3-yl]amino}phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 6-fluoro-N-[2-methyl-5-(5-{[2-(2,2,2-trifluoroethoxy)ethoxy]methyl}-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-[2-(morpholin-4-yl)-1,3-thiazol-4-yl]imidazo[1,2-a]pyridine-3-carboxamide; methyl N-[(3-{4-methyl-3-[7-(3-oxobutyl)imidazo[1,2-a]pyridine-3-amido]phenyl}-1,2,4-oxadiazol-5-yl)methyl]carbamate; methyl N-[(3-{3-[7-(3-hydroxy-3-methylbutyl)imidazo[1,2-a]pyridine-3-amido]-4-methylphenyl}-1,2,4-oxadiazol-5-yl)methyl]carbamate; 7-fluoro-N-(5-{5-(2-methoxyethoxy)methyl}-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxamide; 6-(3-hydroxy-3-methylbutyl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-{5-[(2-methoxyethoxy)methyl]-1,2,4-oxadiazol-3-yl}phenyl)-6-[1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl]imidazo[1,2-a]pyridine-3-carboxamide; N-{2-fluoro-5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]phenyl}-6-[1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[2-(morpholin-4-yl)ethyl]imidazo[1,2-a]pyridine-3-carboxamide; 6-cyano-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-[2-(3-methylmorpholin-4-yl)ethyl]imidazo[1,2-a]pyridine-3-carboxamide; 7-cyano-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; 6-methoxy-N-(5-{5-[(2-methoxyethoxy)methyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{2-methyl-5-[5-(propan-2-yl)-1,2,4-oxadiazol-3-yl]phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(2-methoxyethoxy)methyl]-1,2,4-oxadiazol-3-yl}-2,4-dimethylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(2-oxo-1,3-oxazolidin-3-yl)imidazo[1,2-a]pyridine-3-carboxamide; 7-fluoro-N-(5-{5-[(2-hydroxy-2-methylpropyl)amino]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(2-hydroxy-2-methylpropyl)amino]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)-6-methylimidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2,2,2-trifluoroethoxy)methyl]imidazo[1,2-a]pyridine-3-carboxamide; 6-[3-(methoxymethyl)-1H-1,2,4-triazol-5-yl]-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(2-methoxyethyl)amino]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(1-hydroxyethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{2-methyl-5-[5-(1,2,2,2-tetrafluoroethyl)-1,2,4-oxadiazol-3-yl]phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(1-fluoroethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-

yl)phenyl]-6-(pyrazin-2-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-(4-methylpyridin-3-yl)imidazo[1,2-a]pyridine-3-carboxamide; 6-cyclopropyl-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; methyl N-[[3-(4-methyl-3-{6-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]methyl]carbamate; N-{5-[5-(2-hydroxybutan-2-yl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-(pyrimidin-5-yl)imidazo[1,2-a]pyridine-3-carboxamide; 6-(1,3-dimethyl-1H-pyrazol-5-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; 6-(1-methyl-1H-pyrazol-5-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(ethylcarbamoyl)methyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(diethylcarbamoyl)methyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-[2-(piperazin-1-yl)ethyl]imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-[2-(morpholin-4-yl)ethyl]imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(1S)-1-acetamidoethyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(3-{5-[(2-methoxyethoxy)methyl]-1,2,4-oxadiazol-3-yl}-2,6-dimethylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; tert-butyl 3-(3-{[5-(5-{[(methoxycarbonyl)amino]methyl}-1,2,4-oxadiazol-3-yl)-2-methylphenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)propanoate; N-{5-[5-(aminomethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide, and N-{5-[5-(2-aminopropan-2-yl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide.

**[0144]** Another aspect provided herein are pharmaceutical compositions that include a therapeutically effective amount of a compound of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If), Formula (IIIf), Formula (Ig) or Formula (IIg), and a pharmaceutically acceptable carrier. In certain embodiments of such pharmaceutical compositions, the pharmaceutical composition is formulated for intravenous administration, intravitreal administration, intramuscular administration, oral administration, rectal administration, transdermal administration, pulmonary administration, inhalation administration, nasal administration, topical administration, ophthalmic administration or otic administration. In other embodiments, such pharmaceutical compositions are in the form of a tablet, a pill, a capsule, a liquid, an inhalant, a nasal spray solution, a suppository, a solution, an emulsion, an ointment, eye drop or ear drop. In other embodiments, such pharmaceutical compositions are formulated for oral administration and are in the form of a tablet, a pill, a capsule, a liquid, a solution, or an emulsion. In other embodiments, such pharmaceutical compositions are formulated for oral administration and are in the form of a tablet, a pill, or a capsule. In other embodiments, such pharmaceutical compositions further include one or more additional therapeutic agents. In

other embodiments, such as aforementioned pharmaceutical compositions further include one or more additional therapeutic agents.

**[0145]** Another aspect provided herein are medicaments for treating a patient with a disease or disorder associated with c-kit or PDGFR kinase activity, or c-kit and PDGFR kinase activity, and such medicaments include a therapeutically effective amount of a compound of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If), Formula (IIf), Formula (Ig) or Formula (IIg). In certain embodiments of this aspect the disease is a mast-cell associated disease, a respiratory disease, an inflammatory disorder, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), an autoimmune disorder, a metabolic disease, a fibrosis disease, a dermatological disease, pulmonary arterial hypertension (PAH) or primary pulmonary hypertension (PPH). In other embodiments of this aspect, the disease is asthma, allergic rhinitis, pulmonary arterial hypertension (PAH), pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, scleroderma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), urticaria, dermatosis, type I diabetes or type II diabetes.

**[0146]** Another aspect provided herein are medicaments for treating a disease mediated by c-kit or PDGFR kinase activity, or c-kit and PDGFR kinase activity, in a patient in need thereof, and such medicaments include a therapeutically effective amount of a compound of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If), Formula (IIf), Formula (Ig) or Formula (IIg), and the disease is a mast-cell associated disease, a respiratory disease, an inflammatory disorder, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), an autoimmune disorder, a metabolic disease, a fibrosis disease, a dermatological disease, pulmonary arterial hypertension (PAH) or primary pulmonary hypertension (PPH).

**[0147]** In certain embodiments of this aspect, the disease is asthma, allergic rhinitis, pulmonary arterial hypertension (PAH), pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, scleroderma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), urticaria, dermatosis, type I diabetes or type II diabetes.

**[0148]** Another aspect provided herein is the use of a compound of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If), Formula (IIf), Formula (Ig) or Formula (IIg) in the manufacture of a medicament for treating a disease or disorder in a patient where c-kit or PDGFR kinase activity, or c-kit and PDGFR kinase activity is implicated.

**[0149]** Another aspect provided herein includes methods for treating a disease or disorder where c-kit or PDGFR kinase activity, or c-kit and PDGFR kinase activity is implicated, wherein the method includes administering to a system or subject in need of such treatment an effective amount of a compound of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If), Formula (IIf), Formula (Ig) or Formula (IIg), or pharmaceutically acceptable salts or pharmaceutical compositions thereof, thereby treating the disease or disorder. In certain embodiments of such methods, the

methods include administering the compound to a cell or tissue system or to a human or animal subject. In certain embodiments of such methods, the disease or condition is a metabolic disease, a fibrotic disease, a respiratory disease, an inflammatory disease or disorder, a dermatological disease or an autoimmune disease. In certain embodiments of such methods, the disease or condition is asthma, allergic rhinitis, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), pulmonary arterial hypertension (PAH), pulmonary fibrosis, liver fibrosis, cardiac fibrosis, scleroderma, urticaria, dermatoses, atopic dermatitis, type I diabetes or type II diabetes.

**[0150]** Another aspect provided herein is a compound of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If), Formula (IIf), Formula (Ig) or Formula (IIg) for use in treating a disease mediated by c-kit, PDGFR $\alpha$ , PDGFR $\beta$  or combination thereof, wherein the disease is selected from a mast-cell associated disease, a respiratory disease, an inflammatory disorder, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), an autoimmune disorder, a metabolic disease, a fibrosis disease, a dermatological disease, pulmonary arterial hypertension (PAH) and primary pulmonary hypertension (PPH). In certain embodiments of this aspect, the disease is selected from a mast-cell associated disease, a respiratory disease, an inflammatory disorder, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), an autoimmune disorder, a metabolic disease, a fibrosis disease, a dermatological disease, pulmonary arterial hypertension (PAH) and primary pulmonary hypertension (PPH). In other embodiments the disease is asthma, allergic rhinitis, pulmonary arterial hypertension (PAH), pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, scleroderma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), urticaria, dermatosis, type I diabetes or type II diabetes.

## DETAILED DESCRIPTION OF THE INVENTION

### Definitions

**[0151]** The terms “alkenyl” or “alkene,” as used herein, refers to a partially unsaturated branched or straight chain hydrocarbon having at least one carbon-carbon double bond. Atoms oriented about the double bond are in either the cis (Z) or trans (E) conformation. As used herein, the terms “C<sub>2</sub>-C<sub>3</sub>alkenyl”, “C<sub>2</sub>-C<sub>4</sub>alkenyl”, “C<sub>2</sub>-C<sub>5</sub>alkenyl”, “C<sub>2</sub>-C<sub>6</sub>alkenyl”, “C<sub>2</sub>-C<sub>7</sub>alkenyl”, and “C<sub>2</sub>-C<sub>8</sub>alkenyl” refer to an alkenyl group containing at least 2, and at most 3, 4, 5, 6, 7 or 8 carbon atoms, respectively. If not otherwise specified, an alkenyl group generally is a C<sub>2</sub>-C<sub>6</sub> alkenyl. Non-limiting examples of alkenyl groups, as used herein, include ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl and the like.

**[0152]** The term “alkyl,” as used herein, refers to a saturated branched or straight chain hydrocarbon. In certain embodiments such alkyl groups are optionally substituted. As used herein, the terms “C<sub>1</sub>-C<sub>3</sub>alkyl”, “C<sub>1</sub>-C<sub>4</sub>alkyl”, “C<sub>1</sub>-C<sub>5</sub>alkyl”, “C<sub>1</sub>-C<sub>6</sub>alkyl”, “C<sub>1</sub>-C<sub>7</sub>alkyl” and “C<sub>1</sub>-C<sub>8</sub>alkyl” refer to an alkyl group containing at least 1, and at most 3, 4, 5, 6, 7 or 8 carbon atoms, respectively. If not otherwise specified, an alkyl group generally is a C<sub>1</sub>-C<sub>6</sub> alkyl. Non-limiting examples of alkyl groups as used herein include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, hexyl, heptyl, octyl, nonyl, decyl and the like.



**[0153]** The term “alkoxy,” as used herein, refers to the group —OR<sub>a</sub>, where R<sub>a</sub> is an alkyl group as defined herein. As used herein, the terms “C<sub>1</sub>-C<sub>3</sub>alkoxy”, “C<sub>1</sub>-C<sub>4</sub>alkoxy”, “C<sub>1</sub>-C<sub>5</sub>alkoxy”, “C<sub>1</sub>-C<sub>6</sub>alkoxy”, “C<sub>1</sub>-C<sub>7</sub>alkoxy” and “C<sub>1</sub>-C<sub>8</sub>alkoxy” refer to an alkoxy group wherein the alkyl moiety contains at least 1, and at most 3, 4, 5, 6, 7 or 8, carbon atoms. Non-limiting examples of alkoxy groups, as used herein, include methoxy, ethoxy, n-propoxy, isopropoxy, n-butyloxy, t-butyloxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, decyloxy and the like.

**[0154]** The term “cycloalkyl,” as used herein, refers to a saturated, monocyclic, fused bicyclic, fused tricyclic, spirocyclic or bridged polycyclic ring assembly. As used herein, the terms “C<sub>3</sub>-C<sub>5</sub>cycloalkyl”, “C<sub>3</sub>-C<sub>6</sub>cycloalkyl”, “C<sub>3</sub>-C<sub>7</sub>cycloalkyl”, “C<sub>3</sub>-C<sub>8</sub>cycloalkyl”, “C<sub>3</sub>-C<sub>9</sub>cycloalkyl” and “C<sub>3</sub>-C<sub>10</sub>cycloalkyl” refer to a cycloalkyl group wherein the saturated monocyclic, fused bicyclic or bridged polycyclic ring assembly contain at least 3, and at most 5, 6, 7, 8, 9 or 10, carbon atoms. Non-limiting examples of cycloalkyl groups, as used herein, include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, and the like.

**[0155]** The term “halo,” as used herein, refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I) substituents.

**[0156]** The terms “haloalkyl” or “halo-substituted alkyl,” as used herein, refers to an alkyl group as defined herein, substituted with one or more halo groups as defined herein. The halo groups are the same or different. The haloalkyl can be monohaloalkyl, dihaloalkyl or polyhaloalkyl, including perhaloalkyl. A perhalo-alkyl refers to an alkyl having all hydrogen atoms replaced with halo atoms. A monohaloalkyl can have one iodo, bromo, chloro or fluoro within the alkyl group. Dihaloalkyl and polyhaloalkyl groups can have two or more of the same halo atoms or a combination of different halo groups within the alkyl. Such haloalkyl groups are also referred to herein as “C<sub>1</sub>-C<sub>3</sub>haloalkyl”, “C<sub>1</sub>-C<sub>4</sub>haloalkyl”, “C<sub>1</sub>-C<sub>5</sub>haloalkyl”, “C<sub>1</sub>-C<sub>6</sub>haloalkyl”, “C<sub>1</sub>-C<sub>7</sub>haloalkyl” and “C<sub>1</sub>-C<sub>8</sub>haloalkyl” wherein the alkyl group contains at least 1, and at most 3, 4, 5, 6, 7 or 8 carbon atoms, respectively. Non-limiting examples of such branched or straight chained haloalkyl groups, as used herein, include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. In certain embodiments, a haloalkyl group is trifluoromethyl.

**[0157]** The term “heteroaryl,” as used herein, refers to a 5-6 membered heteroaromatic monocyclic ring having 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, an 8-10 membered fused bicyclic ring having 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur and where at least one of the rings is aromatic, or a 12-14 membered fused tricyclic ring having 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur and where at least one of the rings is aromatic. Such fused bicyclic and tricyclic ring systems may be fused to one or more aryl, cycloalkyl, or heterocycloalkyl rings. Non-limiting examples of heteroaryl groups, as used herein, include 2- or 3-furyl; 1-, 2-, 4-, or 5-imidazolyl; 3-, 4-, or 5-isothiazolyl; 3-, 4-, or 5-isoxazolyl; 2-, 4-, or 5-oxazolyl; 4- or 5-1,2,3-oxadiazolyl; 2- or 3-pyrazinyl; 1-, 3-, 4-, or 5-pyrazolyl; 3-, 4-, 5- or 6-pyridazinyl; 2-, 3-, or 4-pyridyl; 2-, 4-, 5- or 6-pyrimidinyl; 1-, 2- or 3-pyrrolyl; 1- or 5-tetrazolyl; 2- or 5-1,3,4-thiadiazolyl; 2-, 4-, or 5-thiazolyl; 2- or 3-thienyl; 2-,

4- or 6-1,3,5-triazinyl; 1-, 3- or 5-1,2,4-triazolyl; 1-, 4- or 5-1,2,3-triazolyl; 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-acridinyl; 1-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-benzo[g]isoquinoline; 2-, 4-, 5-, 6-, or 7-benzoxazolyl; 1-, 2-, 4-, 5-, 6-, or 7-benzimidazolyl; 2-, 4-, 5-, 6-, or 7-benzothiazolyl; 2-, 3-, 4-, 5-, 6-, 7-benzo[b]thienyl; 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-benzo[b]oxepine; 2-, 4-, 5-, 6-, 7-, or 8-benzoxazinyl; 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-carbazolyl; 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl; 2-, 4-, or 5-4H-imidazo[4,5-d]thiazolyl; 2-, 3-, 5-, or 6-imidazo[2,1-b]thiazolyl; 2-, 3-, 6-, or 7-imidazo[1,2-b][1,2,4]triazinyl; 1-, 3-, 4-, 5-, 6-, or 7-indazolyl; 1-, 2-, 3-, 5-, 6-, 7-, or 8-indolizyl; 1-, 2-, 3-, 4-, 5-, 6-, or 7-indolyl; 1-, 2-, 3-, 4-, 5-, 6-, or 7-isoidolyl; 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolyl; 2-, 3-, 4-, 5-, 6-, or 7-naphthyridinyl; 1-, 2-, 4-, 5-, 6-, 7-, 8-, or 9-perimidinyl; 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenanthridinyl; 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-phenathrolinyl; 1-, 2-, 3-, 4-, 6-, 7-, 8-, or 9-phenazinyl; 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenothiazinyl; 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenoxazinyl; 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl; 2-, 4-, 6-, or 7-pteridinyl; 2-, 6-, 7-, or 8-purinyl; 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10-, or 11-7H-pyrazino[2,3-c]carbazolyl; 2-, 3-, 5-, 6-, or 7-furo[3,2-b]pyranyl; 1-, 3-, or 5-1H-pyrazolo[4,3-d]oxazolyl; 2-, 3-, 5-, or 8-pyrazino[2,3-d]pyridazinyl; 1-, 2-, 3-, 4-, 5-, or 8-5H-pyrido[2,3-d]-o-oxazinyl; 1-, 2-, 3-, 4-, 6-, 7-, 8-, or 9-quinolizyl; 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl; 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinazolinyl; 2-, 3-, 4-, or 5-thieno[2,3-b]furanlyl, and 1-, 3-, 6-, 7-, 8-, or 9-furo[3,4-c]cinnolinyl.

**[0158]** The term “hetero atoms,” as used herein, refers to nitrogen (N), oxygen (O) or sulfur (S) atoms.

**[0159]** The term “heterocycloalkyl,” as used herein refers to a saturated 3-6 membered monocyclic hydrocarbon ring structure, a saturated 6-9 membered fused bicyclic hydrocarbon ring structure, or a saturated 10-14 membered fused tricyclic hydrocarbon ring structure, wherein one to four of the ring carbons of the hydrocarbon ring structure are replaced by one to four groups independently selected from —O—, —NR—, or —S—, wherein R is hydrogen, C<sub>1</sub>-C<sub>4</sub>alkyl or an amino protecting group.

**[0160]** Non-limiting examples of heterocycloalkyl groups, as used herein, include aziridinyl, aziridin-1-yl, aziridin-2-yl, aziridin-3-yl, oxiranyl, oxiran-2-yl, oxiran-3-yl, thiiranyl, thiiran-2-yl, thiiran-3-yl, azetadinyl, azetadin-1-yl, azetadin-2-yl, azetadin-3-yl, oxetanyl, oxetan-2-yl, oxetan-3-yl, oxetan-4-yl, thietanyl, thietan-2-yl, thietan-3-yl, thietan-4-yl, pyrrolidinyl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolidin-4-yl, pyrrolidin-5-yl, tetrahydrofuranlyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrofuran-4-yl, tetrahydrofuran-5-yl, tetrahydrothienyl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, tetrahydrothien-4-yl, tetrahydrothien-5-yl, piperidinyl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperidin-5-yl, piperidin-6-yl, tetrahydropyranlyl, tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydropyran-5-yl, tetrahydropyran-6-yl, tetrahydrothiopyranlyl, tetrahydrothiopyran-2-yl, tetrahydrothiopyran-3-yl, tetrahydrothiopyran-4-yl, tetrahydrothiopyran-5-yl, tetrahydrothiopyran-6-yl, piperazinyl, piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, piperazin-4-yl, piperazin-5-yl, piperazin-6-yl, morpholinyl, morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, morpholin-5-yl, morpholin-6-yl, thiomorpholinyl, thiomorpholin-2-yl, thiomorpholin-3-yl, thiomorpholin-4-yl, thiomorpholin-5-yl, thiomorpholin-6-yl, oxathianyl, oxathian-2-yl, oxathian-3-yl, oxathian-5-yl, oxathian-6-yl, dithianyl, dithian-2-yl, dithian-3-yl, dithian-5-yl, dithian-6-yl, azepanyl, azepan-1-

yl, azepan-2-yl, azepan-3-yl, azepan-4-yl, azepan-5-yl, azepan-6-yl, azepan-7-yl, oxepanyl, oxepan-2-yl, oxepan-3-yl, oxepan-4-yl, oxepan-5-yl, oxepan-6-yl, oxepan-7-yl, thiepanyl, thiepan-2-yl, thiepan-3-yl, thiepan-4-yl, thiepan-5-yl, thiepan-6-yl, thiepan-7-yl, dioxolanyl, dioxolan-2-yl, dioxolan-4-yl, dioxolan-5-yl, thioxanyl, thioxan-2-yl, thioxan-3-yl, thioxan-4-yl, thioxan-5-yl, dithiolanyl, dithiolan-2-yl, dithiolan-4-yl, dithiolan-5-yl, pyrrolinyl, pyrrolin-1-yl, pyrrolin-2-yl, pyrrolin-3-yl, pyrrolin-4-yl, pyrrolin-5-yl, imidazolanyl, imidazolin-1-yl, imidazolin-3-yl, imidazolin-4-yl, imidazolin-5-yl, imidazolidinyl, imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-3-yl, imidazolidin-4-yl, imidazolidin-5-yl, pyrazolinyl, pyrazolin-1-yl, pyrazolin-3-yl, pyrazolin-4-yl, pyrazolin-5-yl, pyrazolidinyl, pyrazolidin-1-yl, pyrazolidin-2-yl, pyrazolidin-3-yl, pyrazolidin-4-yl, pyrazolidin-5-yl, hexahydro-1,4-diazepinyl, dihydrofuranyldihydropyranyl, 1,2,3,6-tetrahydropyridinyl, 2H-pyranyl, 4H-pyranyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, pyrrolidinyl-2-one, piperidinyl-3-one piperidinyl-2-one, piperidinyl-4-one, and 2H-pyrrolyl.

**[0161]** The term “acceptable” with respect to a compound, formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

**[0162]** The term “administration” or “administering” of the subject compound means providing a compound of Formula (I) or Formula (II), a pharmaceutically acceptable salt, a pharmaceutically acceptable solvate, or solvate thereof to a subject in need of treatment.

**[0163]** The term “autoimmune disease,” or “autoimmune disorder,” as used herein, refers diseases wherein cells uncontrollably attack the body’s own tissues and organs (autoimmunity), producing inflammatory reactions and other serious symptoms and diseases. Non-limiting examples of autoimmune diseases include idiopathic thrombocytopenic purpura, hemolytic anemia, systemic lupus erythematosus, rheumatoid arthritis (RA), multiple sclerosis (MS), immune-mediated or type 1 diabetes mellitus, immune mediated glomerulonephritis, scleroderma, pernicious anemia, alopecia, pemphigus, sclerophagus vulgaris, myasthenia gravis, inflammatory bowel diseases, Crohn’s disease, psoriasis, autoimmune thyroid diseases, and Hashimoto’s disease, Hashimoto’s thyroiditis, dermatomyositis, goodpasture syndrome, myasthenia gravis pseudoparalytica, ophthalmia sympathica, phakogene uveitis, chronic aggressive hepatitis, primary biliary cirrhosis, autoimmune hemolytic anemiy, Werlof disease, vitiligo vulgaris, Behcet’s disease, collagen disease, uveitis, Sjogren’s syndrome, autoimmune myocarditis, autoimmune hepatic diseases, autoimmune gastritis, pemphigus, Guillain-Barre syndrome, and HTLV-1-associated myelopathy.

**[0164]** The term “carrier,” as used herein, refers to chemical compounds or agents that facilitate the incorporation of a compound described herein into cells or tissues.

**[0165]** The terms “co-administration” or “combined administration” or the like as used herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

**[0166]** The term “dermatological disease” or “dermatological disorder,” as used herein refers to a skin disorder. Such dermatological disorders include, but are not limited to, pro-

liferative or inflammatory disorders of the skin such as, atopic dermatitis, bullous disorders, collagenoses, contact dermatitis eczema, Kawasaki Disease, rosacea, Sjogren-Larsson Syndrome, actinic keratosis, basal cell carcinoma and urticaria.

**[0167]** The term “diluent,” as used herein, refers to chemical compounds that are used to dilute a compound described herein prior to delivery. Diluents can also be used to stabilize compounds described herein.

**[0168]** The terms “effective amount” or “therapeutically effective amount,” as used herein, refer to a sufficient amount of a compound described herein being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate “effective” amount in any individual case may be determined using techniques, such as a dose escalation study.

**[0169]** The terms “enhance” or “enhancing,” as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term “enhancing” refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An “enhancing-effective amount,” as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

**[0170]** The terms “fibrosis” or “fibrosis disease,” as used herein, refers to conditions that follow acute or chronic inflammation and are associated with the abnormal accumulation of cells and/or collagen and include but are not limited to fibrosis of individual organs or tissues such as the heart, kidney, joints, lung, or skin, and includes such disorders as idiopathic pulmonary fibrosis and cryptogenic fibrosing alveolitis.

**[0171]** The term “inflammatory disease or disorders,” as used herein, refers to those diseases or conditions that are characterized by one or more of the signs of pain (dolor, from the generation of noxious substances and the stimulation of nerves), heat (calor, from vasodilatation), redness (rubor, from vasodilatation and increased blood flow), swelling (tumor, from excessive inflow or restricted outflow of fluid), and loss of function (functio laesa, which may be partial or complete, temporary or permanent). Inflammation takes many forms and includes, but is not limited to, inflammation that is one or more of the following: acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing, focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing, seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative. Inflammatory disorders further include, without being limited to those affecting the blood vessels (polyarteritis; temporal arthritis); joints (arthritis: crystalline, osteo-, psoriatic, reactive, rheumatoid, Reiter’s); gastrointestinal tract (Disease,); skin (dermatitis); or multiple organs and tissues (systemic lupus erythematosus).

**[0172]** As used herein, the term “inhibit”, “inhibition” or “inhibiting” refers to the reduction or suppression of a given

condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

**[0173]** The term “pharmaceutically acceptable,” as used herein, refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compounds described herein. Such materials are administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

**[0174]** The term “pharmaceutically acceptable carrier,” as used herein, includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (e.g., antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington’s Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289-1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

**[0175]** The term “pharmaceutically acceptable salt,” as used herein, refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compounds described herein.

**[0176]** The terms “combination” or “pharmaceutical combination,” as used herein mean a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term “fixed combination” means that the active ingredients, by way of example, a compound of Formula (I) or Formula (II) and an additional therapeutic agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term “non-fixed combination” means that the active ingredients, by way of example, a compound of Formula (I) or Formula (II) and an additional therapeutic agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

**[0177]** The terms “composition” or “pharmaceutical composition,” as used herein, refers to a mixture of at least one compound, such as the compounds of Formula (I) or Formula (II) provided herein, with at least one and optionally more than one other pharmaceutically acceptable chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients.

**[0178]** The term “respiratory disease,” as used herein, refers to diseases affecting the organs that are involved in breathing, such as the nose, throat, larynx, trachea, bronchi, and lungs. Respiratory diseases include, but are not limited to, asthma, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, occupa-

tional asthma, steroid-resistant asthma, seasonal asthma, seasonal allergic rhinitis, perennial allergic rhinitis, chronic obstructive pulmonary disease, including chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis, and hypoxia.

**[0179]** The term “subject” or “patient,” as used herein, encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, humans, chimpanzees, apes, monkeys, cattle, horses, sheep, goats, swine; rabbits, dogs, cats, rats, mice, guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like. Frequently the subject is a human, and may be a human who has been diagnosed as in need of treatment for a disease or disorder disclosed herein.

**[0180]** As used herein, a subject is “in need of” a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

**[0181]** The term “c-kit inhibitor,” as used herein, refers to a compound which inhibits c-kit kinase.

**[0182]** The term “disease or disorder associated with c-kit activity,” as used herein, refers to any disease state associated with a c-kit kinase. Such diseases or disorders include, but are not limited to, a mast-cell associated disease, inflammatory diseases, respiratory diseases, fibrosis diseases, a dermatological disease, metabolic diseases and autoimmune diseases, such as, by way of example only, asthma, dermatitis, allergic rhinitis, pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, scleroderma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), urticaria, rheumatoid arthritis, multiple sclerosis, uticaria, pulmonary arterial hypertension (PAH), primary pulmonary hypertension (PPH), dermatosis, diabetes, type I diabetes and type II diabetes.

**[0183]** The term “PDGFR inhibitor,” as used herein, refers to a compound which inhibits PDGFR kinase.

**[0184]** The term “disease or disorder associated with PDGFR activity,” as used herein, refers to any disease state associated with a PDGFR kinase. Such diseases or disorders include, but are not limited to, inflammatory diseases, respiratory diseases, fibrosis diseases, metabolic diseases and autoimmune diseases, such as, by way of example only, asthma, dermatitis, allergic rhinitis, scleroderma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), urticaria, rheumatoid arthritis, multiple sclerosis, pulmonary arterial hypertension and diabetes.

**[0185]** The term “an optical isomer” or “a stereoisomer,” as used herein, refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. The term “chiral” refers to molecules which have the property of non-superimposability on their mirror image partner, while the term “achiral” refers to molecules which are superimposable on their mirror image partner. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound. “Enantiomers” are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a “racemic” mixture. The term is used to designate a racemic mixture where appropriate. “Diastereoisomers” are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R—S system. When a compound is a pure enantiomer the stereochemistry

at each chiral carbon may be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (−) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-.

**[0186]** The term “a therapeutically effective amount” of a compound of the present invention, as used herein, refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a subject, is effective to (1) at least partially alleviating, inhibiting, preventing and/or ameliorating a condition, or a disorder or a disease (i) mediated by c-kit kinase or c-kit and PDGFR kinases, or (ii) associated with c-kit kinase or c-kit and PDGFR kinase activity, or (iii) characterized by activity (normal or abnormal) of c-kit kinase or c-kit and PDGFR kinases; or (2) reducing or inhibiting the activity of c-kit kinase or c-kit and PDGFR kinases; or (3) reducing or inhibiting the expression of c-kit kinase or c-kit and PDGFR kinases. In another non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reducing or inhibiting the activity of c-kit kinase or c-kit and PDGFR kinases; or at least partially reducing or inhibiting the expression of c-kit kinase or c-kit and PDGFR kinases.

**[0187]** The terms “treat,” “treating” or “treatment,” as used herein, refers to methods of alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

**[0188]** In addition, as used herein, the term “treat,” “treating” or “treatment” of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment “treat,” “treating” or “treatment” refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, “treat,” “treating” or “treatment” refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, “treat,” “treating” or “treatment” refers to preventing or delaying the onset or development or progression of the disease or disorder.

**[0189]** The compound names provided herein were obtained using ChemDraw Ultra 10.0 (CambridgeSoft®) or JChem version 5.3.1 (ChemAxon).

**[0190]** Unless specified otherwise, the term “compounds of the present invention”, “compounds of the invention”, “compounds provided herein” or “compounds of Formula (I) and Formula (II)” refers to compounds of Formula (I) and Formula (II), and subformulae thereof (such as Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) and Formula (IIf)), and pharmaceutically acceptable salts, hydrates or solvates, stereoisomers (including diastereoisomers and enantiomers), tautomers and isotopically labeled compounds (including deuterium substitutions) thereof. Compounds of the present invention further comprise polymorphs of compounds of Formula (I) and Formula (II) (or subformulae thereof) and salts thereof.

**[0191]** As used herein, the term “a,” “an,” “the” and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

**[0192]** All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g. “such as”) provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

**[0193]** Various enumerated embodiments of the invention are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments of the present invention.

#### DESCRIPTION OF THE PREFERRED EMBODIMENTS

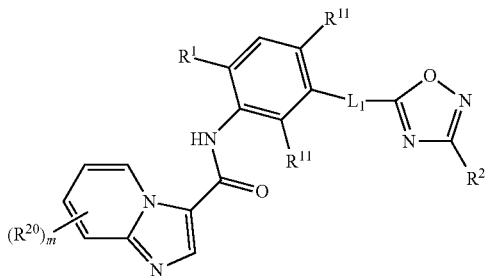
**[0194]** Provided herein are compounds, pharmaceutically acceptable salts, solvates, N-oxides and isomers thereof, that are inhibitors of c-kit kinase or c-kit and PDGFR kinases. Certain embodiments of compounds provided herein have an  $IC_{50}$  for PDGFR inhibition to  $IC_{50}$  for c-kit inhibition ratio ( $IC_{50} PDGFR/IC_{50} c-kit$ ) in the range of 750 to 1000. Certain embodiments of compounds provided herein have an  $IC_{50}$  for PDGFR inhibition to  $IC_{50}$  for c-kit inhibition ratio ( $IC_{50} PDGFR/IC_{50} c-kit$ ) in the range of 500 to 750. Certain embodiments of compounds provided herein have an  $IC_{50}$  for PDGFR inhibition to  $IC_{50}$  for c-kit inhibition ratio ( $IC_{50} PDGFR/IC_{50} c-kit$ ) in the range of 250 to 500. Certain embodiments of compounds provided herein have an  $IC_{50}$  for PDGFR inhibition to  $IC_{50}$  for c-kit inhibition ratio ( $IC_{50} PDGFR/IC_{50} c-kit$ ) in the range of 100 to 250. Certain embodiments of compounds provided herein have an  $IC_{50}$  for PDGFR inhibition to  $IC_{50}$  for c-kit inhibition ratio ( $IC_{50} PDGFR/IC_{50} c-kit$ ) in the range of 75 to 100. Certain embodiments of compounds provided herein have an  $IC_{50}$  for PDGFR inhibition to  $IC_{50}$  for c-kit inhibition ratio ( $IC_{50} PDGFR/IC_{50} c-kit$ ) in the range of 50 to 75. Certain embodiments of compounds provided herein have an  $IC_{50}$  for PDGFR inhibition to  $IC_{50}$  for c-kit inhibition ratio ( $IC_{50} PDGFR/IC_{50} c-kit$ ) in the range of 25 to 50. Certain embodiments of compounds provided herein have an  $IC_{50}$  for PDGFR inhibition to  $IC_{50}$  for c-kit inhibition ratio ( $IC_{50} PDGFR/IC_{50} c-kit$ ) in the range of 10 to 25. Certain embodiments of compounds provided herein have an  $IC_{50}$  for PDGFR inhibition to  $IC_{50}$  for c-kit inhibition ratio ( $IC_{50} PDGFR/IC_{50} c-kit$ ) in the range of 7.5 to 10. Certain embodi-

ments of compounds provided herein have an  $IC_{50}$  for PDGFR inhibition to  $IC_{50}$  for c-kit inhibition ratio ( $IC_{50}^{PDGFR}/IC_{50}^{c-kit}$ ) in the range of 5 to 7.5. Certain embodiments of compounds provided herein have an  $IC_{50}$  for PDGFR inhibition to  $IC_{50}$  for c-kit inhibition ratio ( $IC_{50}^{PDGFR}/IC_{50}^{c-kit}$ ) in the range of 2.5 to 5. Certain embodiments of compounds provided herein have an  $IC_{50}$  for PDGFR inhibition to  $IC_{50}$  for c-kit inhibition ratio ( $IC_{50}^{PDGFR}/IC_{50}^{c-kit}$ ) in the range of 1 to 2.5. Certain embodiments of compounds provided herein have an  $IC_{50}$  for PDGFR inhibition to  $IC_{50}$  for c-kit inhibition ratio ( $IC_{50}^{PDGFR}/IC_{50}^{c-kit}$ ) in the range of 0.95 to 2.5.

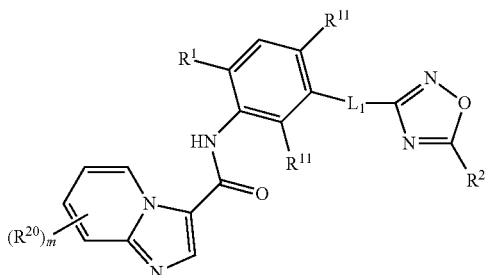
**[0195]** Also provided herein are pharmaceutical compositions that include such compounds. Further provided herein are methods for the treatment of diseases and/or disorders associated with c-kit kinase or c-kit and PDGFR kinases using such compounds and pharmaceutical compositions.

**[0196]** The c-kit kinase, or c-kit and PDGFR kinase, inhibitors of the present invention are compounds having the structure of Formula (I) or Formula (II), and pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof:

Formula (I)



Formula (II)



wherein:

**[0197]**  $m$  is 1 and  $R^{20}$  is selected from H, halo,  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ haloalkyl,  $C_1$ - $C_6$ haloalkoxy, deuterium, deuterated  $C_1$ - $C_6$ alkyl,  $-CN$ ,  $-(CR^9)_nOR^4$ ,  $-C(O)R^4$ ,  $-(CR^9)_2C(=O)OR^4$ ,  $R^8$ ,  $-(CR^9)_nR^8$ ,  $-((CR^9)_nO)R^4$ ,  $-(CR^9)_nO(CR^9)_nR^6$ ,  $-(CR^9)_nC(=O)R^4$ ,  $-C(=O)NR^4$ ,  $(R^4)_2$ ,  $-(CR^9)_nOR^4$ ,  $-OR^4$  and  $-(CR^9)_nCN$ ;

**[0198]**  $m$  is 4 and  $R^{20}$  is deuterium;

**[0199]**  $R^1$  is selected from  $C_1$ - $C_6$ alkyl and halo;

**[0200]** each  $R^{11}$  is independently selected from H, halo and  $C_1$ - $C_6$ alkyl;

**[0201]**  $L_1$  is a bond,  $-NH-$  or  $-C(O)NH-$ ;

**[0202]**  $R^2$  is selected from  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ haloalkyl,  $C_2$ - $C_8$ alkenyl,  $-(CR^9)_nOR^4$ ,  $-(CR^9)_nR^6$ ,  $-(CR^9)_nS$

$(=O)_2NR^4$ ,  $-(CR^9)_nCN$ ,  $-(CR^9)_nC(=O)R^4$ ,  $-(CR^9)_nOC(=O)R^4$ ,  $-(CR^9)_nC(=O)OR^4$ ,  $-(CR^9)_nOC(=O)NR^4$ ,  $-(CR^9)_nOC(=O)OR^4$ ,  $-(CR^9)_nO(CR^9)_nOR^4$ ,  $-(CR^9)_nO(CR^9)_nR^6$ ,  $-(CR^9)_nOCR^9R^6$ ,  $-(CR^9)_nCR^9R^5R^6$ ,  $-(CR^9)_nCR^9R^6R^6$ ,  $-(CR^9)_nCR^9R^5R^6$ ,  $-(CR^9)_nCR^9R^6R^6$ ,  $-(CR^9)_nNR^4$ ,  $-(CR^9)_nNR^4$ ,  $-(CR^9)_nNR^4C(=O)R^4$ ,  $-(CR^9)_nNR^4C(=O)OR^4$ ,  $-(CR^9)_nNR^4C(=O)NR^4$ ,  $-(CR^9)_nNR^4C(=O)R^6$ ,  $-(CR^9)_nNR^4S(=O)R^4$ ,  $-(CR^9)_nNR^4C(=O)O(CR^9)_nOR^4$ ,  $-(CR^9)_nNR^4C(=O)(CR^9)_nOR^4$ ,  $-(CR^9)_nNR^4C(=O)R^6$ ,  $-(CR^9)_nNR^4C(=O)(CR^9)_nR^6$ , and  $-(CR^9)_nNR^4C(=O)O(CR^9)_nR^6$ ;

**[0203]** each  $R^4$  is independently selected from H and  $C_1$ - $C_6$ alkyl;

**[0204]** each  $R^5$  is independently selected from  $-NHC(O)OR^4$ ,  $-OR^4$  and  $-(CR^9)_nOR^4$ ;

**[0205]** each  $R^6$  is a  $C_1$ - $C_6$ haloalkyl;

**[0206]** each  $R^9$  is independently selected from H and  $C_1$ - $C_6$ alkyl;

**[0207]**  $R^8$  is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted  $C_3$ - $C_8$ cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted  $C_3$ - $C_8$ cycloalkyl, an oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

**[0208]** wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted  $C_3$ - $C_8$ cycloalkyl and substituted 4-6 membered heterocycloalkyl of  $R^8$  are substituted with 1-3 substituents independently selected from  $C_1$ - $C_6$ alkyl, halo,  $-(C(R^9)_2)_nOR^4$ ,  $-C(O)NR^4$ ,  $-NR^4$ ,  $-R^{10}$ ,  $-(C(R^9)_2)_nR^{10}$ ,  $-OR^4$ ,  $-(C(R^9)_2)_nC(O)OR^4$  and  $-S(O)_2R^4$ ;

**[0209]**  $R^{10}$  is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted  $C_3$ - $C_8$ cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, and a substituted  $C_3$ - $C_8$ cycloalkyl,

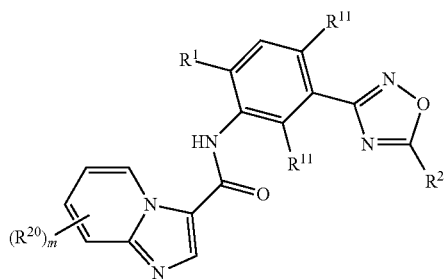
**[0210]** wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N,

substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl and substituted 4-6 membered heterocycloalkyl of R<sup>10</sup> are substituted with 1-3 substituents independently selected from C<sub>1</sub>-C<sub>6</sub>alkyl, and  $-(C(R^9)_2)_mOR^4$ ;

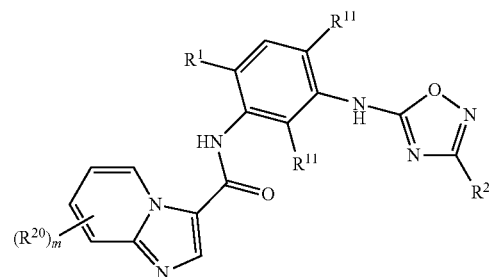
[0211] t is 1, 2 or 3, and

[0212] each n is independently selected from 1, 2, 3 and 4.

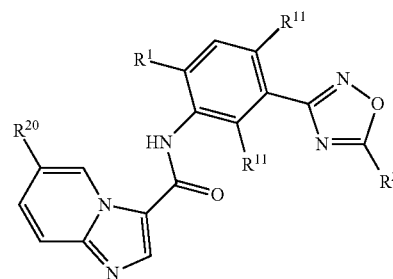
[0213] In certain embodiments of compounds of Formula (I) or Formula (II), and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, the compound of Formula (I) or Formula (II) is a compound having a structure of Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), Formula (Ig) or Formula (IIg):



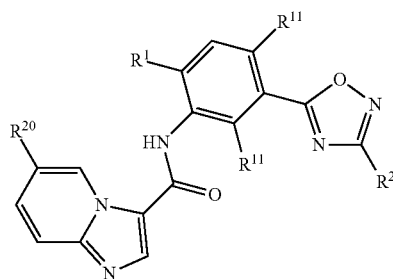
Formula (Ia)



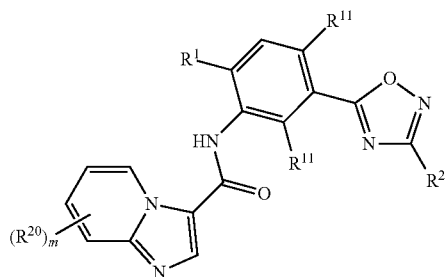
Formula (Ib)



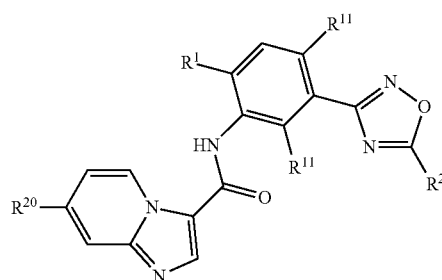
Formula (Ic)



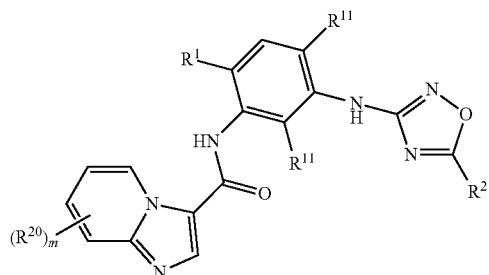
Formula (Id)



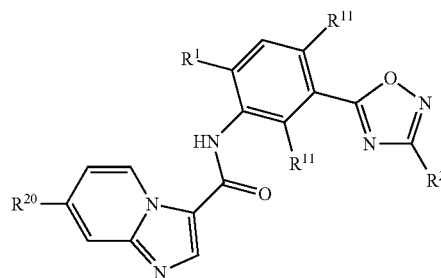
Formula (IIa)



Formula (IIb)



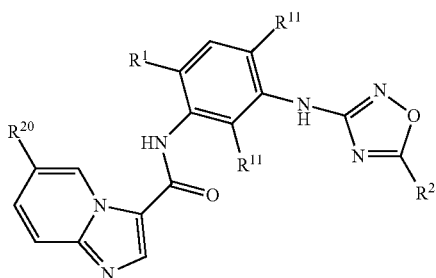
Formula (IIc)



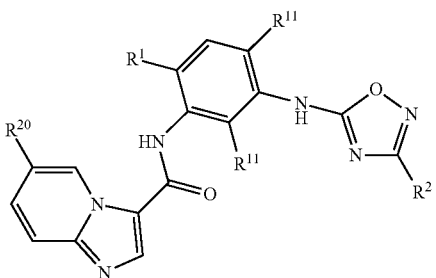
Formula (IId)

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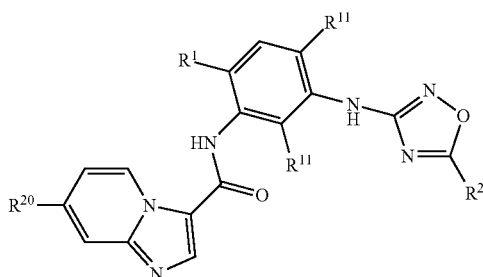
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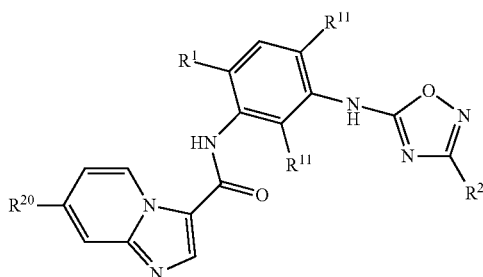
Formula (Ie)



Formula (IIf)



Formula (IIg)



Formula (IIh)

wherein:

[0214] *m* is 1 and R<sup>20</sup> is selected from H, halo, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>haloalkoxy, deuterium, deuterated C<sub>1</sub>-C<sub>6</sub>alkyl, —CN, —(CR<sup>9</sup>)<sub>*n*</sub>OR<sup>4</sup>, —C(O)R<sup>4</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>C(=O)OR<sup>4</sup>, R<sup>8</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>R<sup>8</sup>, —((CR<sup>9</sup>)<sub>*n*</sub>O)<sub>*r*</sub>R<sup>4</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>O(CR<sup>9</sup>)<sub>*n*</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>C(=O)R<sup>4</sup>, —C(=O)N(R<sup>4</sup>)<sub>2</sub>, —(CR<sup>9</sup>)<sub>*n*</sub>OR<sup>4</sup>, —OR<sup>4</sup> and —(CR<sup>9</sup>)<sub>*n*</sub>CN;

[0215] or *m* is 4 and R<sup>20</sup> is deuterium;

[0216] R<sup>1</sup> is selected from C<sub>1</sub>-C<sub>6</sub>alkyl and halo;

[0217] each R<sup>11</sup> is independently selected from H, halo and C<sub>1</sub>-C<sub>6</sub>alkyl;

[0218] R<sup>2</sup> is selected from C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl, —(CR<sup>9</sup>)<sub>*n*</sub>OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>S(=O)<sub>2</sub>NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>CN, —(CR<sup>9</sup>)<sub>*n*</sub>C(=O)R<sup>4</sup>,

—(CR<sup>9</sup>)<sub>*n*</sub>OC(=O)R<sup>4</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>C(=O)OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>C(=O)NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>OC(=O)ONR<sup>4</sup>, (CR<sup>9</sup>)<sub>*n*</sub>OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>O(CR<sup>9</sup>)<sub>*n*</sub>OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>O(CR<sup>9</sup>)<sub>*n*</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>O(CR<sup>9</sup>)<sub>*n*</sub>O(CR<sup>9</sup>)<sub>*n*</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>O(CR<sup>9</sup>)<sub>*n*</sub>R<sup>6</sup>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>CR<sup>9</sup>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>CR<sup>9</sup>R<sup>6</sup>R<sup>6</sup>, —CR<sup>9</sup>R<sup>6</sup>R<sup>6</sup>—CR<sup>9</sup>R<sup>6</sup>R<sup>5</sup>, —CR<sup>9</sup>R<sup>6</sup>NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>NR<sup>4</sup>, —NR<sup>4</sup>(CR<sup>9</sup>)<sub>*n*</sub>OR<sup>4</sup>, —NR<sup>4</sup>(CR<sup>9</sup>)<sub>*n*</sub>R<sup>6</sup>, —NR<sup>4</sup>(CR<sup>9</sup>)<sub>*n*</sub>R<sup>4</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>NR<sup>4</sup>C(=O)R<sup>4</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>NR<sup>4</sup>C(=O)OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>NR<sup>4</sup>C(=O)NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>NR<sup>4</sup>C(=O)R<sup>6</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>NR<sup>4</sup>S(=O)<sub>2</sub>R<sup>4</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>NR<sup>4</sup>C(=O)O(CR<sup>9</sup>)<sub>*n*</sub>OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>NR<sup>4</sup>C(=O)(CR<sup>9</sup>)<sub>*n*</sub>OR<sup>4</sup>, —CR<sup>9</sup>R<sup>6</sup>NR<sup>4</sup>S(=O)<sub>2</sub>R<sup>4</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>NR<sup>4</sup>C(=O)R<sup>6</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>NR<sup>4</sup>C(=O)(CR<sup>9</sup>)<sub>*n*</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>NR<sup>4</sup>C(=O)O(CR<sup>9</sup>)<sub>*n*</sub>R<sup>11</sup>, —(CR<sup>9</sup>)<sub>*n*</sub>NR<sup>4</sup>C(=O)(CR<sup>9</sup>)<sub>*n*</sub>O(CR<sup>9</sup>)<sub>*n*</sub>R<sup>6</sup>, and —(CR<sup>9</sup>)<sub>*n*</sub>NR<sup>4</sup>C(=O)O(CR<sup>9</sup>)<sub>*n*</sub>R<sup>6</sup>;

[0219] each R<sup>4</sup> is independently selected from H and C<sub>1</sub>-C<sub>6</sub>alkyl;

[0220] each R<sup>5</sup> is independently selected from —NHC(O)OR<sup>4</sup>, —OR<sup>4</sup> and —(CR<sup>9</sup>)<sub>*n*</sub>OR<sup>4</sup>;

[0221] each R<sup>6</sup> is a C<sub>1</sub>-C<sub>6</sub>haloalkyl;

[0222] each R<sup>9</sup> is independently selected from H and C<sub>1</sub>-C<sub>6</sub>alkyl;

[0223] R<sup>8</sup> is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

[0224] wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl and substituted 4-6 membered heterocycloalkyl of R<sup>8</sup> are substituted with 1-3 substituents independently selected from C<sub>1</sub>-C<sub>6</sub>alkyl, halo, —(C(R<sup>9</sup>)<sub>2</sub>)<sub>*n*</sub>OR<sup>4</sup>, —C(O)NR<sup>4</sup>, —NR<sup>4</sup>, —R<sup>10</sup>, —(C(R<sup>9</sup>)<sub>2</sub>)<sub>*n*</sub>R<sup>10</sup>, —OW, —(C(R<sup>9</sup>)<sub>2</sub>)<sub>*n*</sub>C(O)OR<sup>4</sup> and —S(O)<sub>2</sub>R<sup>4</sup>;

[0225] R<sup>10</sup> is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, and a substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl,

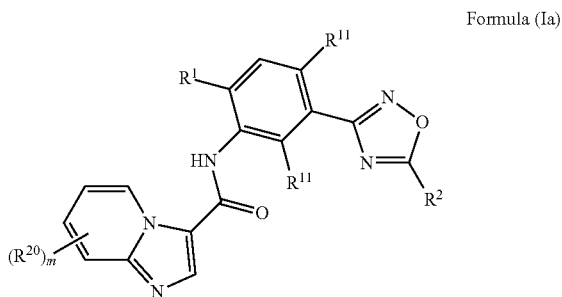
[0226] wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5

membered heteroaryl with 1-4 heteroatoms selected from N, substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl and substituted 4-6 membered heterocycloalkyl of R<sup>10</sup> are substituted with 1-3 substituents independently selected from C<sub>1</sub>-C<sub>6</sub>alkyl, and —(C(R<sup>9</sup>)<sub>2</sub>)<sub>n</sub>OR<sup>4</sup>;

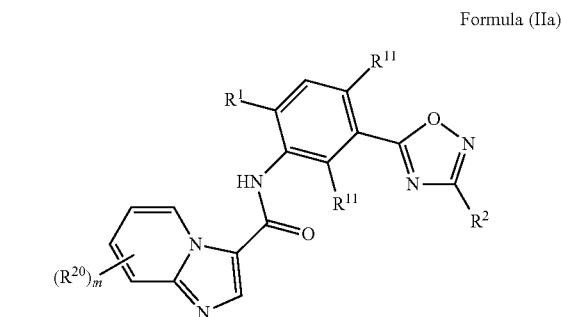
[0227] t is 1, 2 or 3, and

[0228] each n is independently selected from 1, 2, 3 and 4.

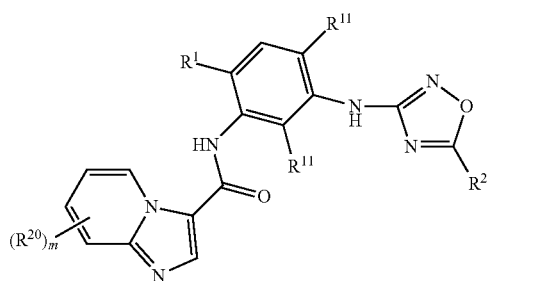
[0229] In certain embodiments of compounds of Formula (I) or Formula (II), and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, the compound of Formula (I) or Formula (II) is a compound having a structure of Formula (Ia), Formula (IIa), Formula (Ib) or Formula (IIb):



Formula (Ia)



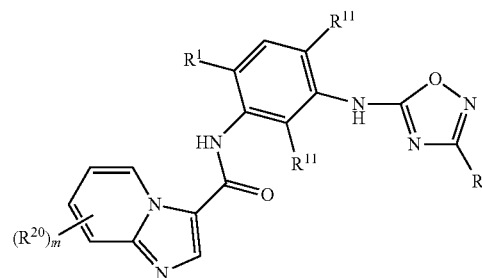
Formula (IIa)



Formula (Ib)

-continued

Formula (IIb)



wherein:

[0230] m is 1 and R<sup>20</sup> is selected from H, halo, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>haloalkoxy, deuterium, deuterated C<sub>1</sub>-C<sub>6</sub>alkyl, —CN, —(CR<sup>9</sup>)<sub>2</sub>OR<sup>4</sup>, —C(O)R<sup>4</sup>, —(CR<sup>9</sup>)<sub>2</sub>C(=O)OR<sup>4</sup>, R<sup>8</sup>, —(CR<sup>9</sup>)<sub>2</sub>R<sup>8</sup>, —((CR<sup>9</sup>)<sub>2</sub>O)<sub>n</sub>R<sup>4</sup>, —(CR<sup>9</sup>)<sub>2</sub>O(CR<sup>9</sup>)<sub>n</sub>R<sup>8</sup>, —(CR<sup>9</sup>)<sub>2</sub>C(=O)R<sup>4</sup>, —C(=O)N(R<sup>4</sup>)<sub>2</sub>, —(CR<sup>9</sup>)<sub>2</sub>OR<sup>4</sup>, —OR<sup>4</sup> and —(CR<sup>9</sup>)<sub>2</sub>CN;

[0231] or m is 4 and R<sup>20</sup> is deuterium;

[0232] R<sup>1</sup> is selected from C<sub>1</sub>-C<sub>6</sub>alkyl and halo;

[0233] each R<sup>11</sup> is independently selected from H, halo and C<sub>1</sub>-C<sub>6</sub>alkyl;

[0234] R<sup>2</sup> is selected from C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl, —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>R<sup>8</sup>, —(CR<sup>9</sup>)<sub>n</sub>S(=O)<sub>2</sub>NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>CN, —(CR<sup>9</sup>)<sub>n</sub>C(=O)R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>OC(=O)R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>C(=O)OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>C(=O)NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>OC(=O)ONR<sup>4</sup>, (CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>CR<sup>5</sup>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>CR<sup>5</sup>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>CR<sup>5</sup>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>CR<sup>5</sup>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>, —NR<sup>4</sup>(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —NR<sup>4</sup>(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —NR<sup>4</sup>(CR<sup>9</sup>)<sub>n</sub>R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>S(=O)<sub>2</sub>R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)O(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>S(=O)<sub>2</sub>R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>S(=O)<sub>2</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)O(CR<sup>9</sup>)<sub>n</sub>R<sup>11</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, and —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)O(CR<sup>9</sup>)<sub>n</sub>R<sup>8</sup>;

[0235] each R<sup>4</sup> is independently selected from H and C<sub>1</sub>-C<sub>6</sub>alkyl;

[0236] each R<sup>5</sup> is independently selected from —NHC(O)OR<sup>4</sup>, —OR<sup>4</sup> and —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>;

[0237] each R<sup>6</sup> is a C<sub>1</sub>-C<sub>6</sub>haloalkyl;

[0238] each R<sup>9</sup> is independently selected from H and C<sub>1</sub>-C<sub>6</sub>alkyl;

[0239] R<sup>8</sup> is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a sub-



stituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

**[0240]** wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl and substituted 4-6 membered heterocycloalkyl of R<sup>8</sup> are substituted with 1-3 substituents independently selected from C<sub>1</sub>-C<sub>6</sub>alkyl, halo,  $-(C(R^9)_2)_nOR^4$ ,  $-C(O)NR^4$ ,  $-NR^4$ ,  $-R^{10}$ ,  $-(C(R^9)_2)_nR^{10}$ ,  $-OR^4$ ,  $-(C(R^9)_2)_nC(O)OR^4$  and  $-S(O)_2R^4$ ;

**[0241]** R<sup>10</sup> is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, and a substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl,

**[0242]** wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl and substituted 4-6 membered heterocycloalkyl of R<sup>10</sup> are substituted with 1-3 substituents independently selected from C<sub>1</sub>-C<sub>6</sub>alkyl, and  $-(C(R^9)_2)_nOR^4$ ;

**[0243]** t is 1, 2 or 3, and

**[0244]** each n is independently selected from 1, 2, 3 and 4.

**[0245]** The compounds of Formula (I) or Formula (II), pharmaceutically acceptable salts, solvates, N-oxides and isomers thereof, and pharmaceutical compositions provided herein also includes all suitable isotopic variations of such compounds, and pharmaceutically acceptable salts, solvates, N-oxides and isomers thereof, and pharmaceutical compositions. Therefore, any formula 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 invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine, and chlorine, such as <sup>2</sup>H, <sup>3</sup>H, <sup>11</sup>C, <sup>13</sup>C, <sup>14</sup>C, <sup>15</sup>N, <sup>18</sup>F, <sup>31</sup>P, <sup>32</sup>P, <sup>35</sup>S, <sup>36</sup>Cl, <sup>125</sup>I respectively.

**[0246]** The invention includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as <sup>3</sup>H and <sup>14</sup>C, or those into which non-radioactive isotopes, such as <sup>2</sup>H and <sup>13</sup>C are present. Such isotopically labeled compounds are useful in metabolic studies (with <sup>14</sup>C), reaction kinetic studies (with, for example <sup>2</sup>H or <sup>3</sup>H), 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. In particular, an <sup>18</sup>F or labeled compound may be particularly

desirable for PET or SPECT studies. Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

**[0247]** Further, substitution with heavier isotopes, particularly deuterium (i.e., <sup>2</sup>H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

**[0248]** Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D<sub>2</sub>O, d<sub>6</sub>-acetone, d<sub>6</sub>-DMSO.

**[0249]** Compounds of the invention, i.e. compounds of Formula (I) and Formula (II) that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of formula (I) by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of formula (I) with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004078163. Hence the invention further provides co-crystals comprising a compound of Formula (I) and Formula (II).

Processes for Making Compounds of Formula (I) or Formula (II)

**[0250]** General procedures for preparing compounds of Formula (I) or Formula (II) are described in the Examples, infra. In the reactions described, reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, may be protected to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice (see e.g., T. W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry," John Wiley and Sons, 1991).

**[0251]** In certain embodiments, the compounds of Formula (I) or Formula (II) provided herein are prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound of Formula (I) or Formula (II)

with a stoichiometric amount of an appropriate pharmaceutically acceptable organic acid or inorganic acid or a suitable anion exchange reagent. In other embodiments, a pharmaceutically acceptable base addition salt of compounds of Formula (I) or Formula (II) is prepared by reacting the free acid form of the compound of Formula (I) or Formula (II) with a stoichiometric amount of an appropriate pharmaceutically acceptable organic base or inorganic base or a suitable ion exchange reagent. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable.

**[0252]** Alternatively, the salt forms of the compounds of Formula (I) or Formula (II) are prepared using salts of the starting materials or intermediates. In certain embodiments, the compounds of Formula (I) or Formula (II) are in the form of other salts including, but not limited to, oxalates and trifluoroacetates. In certain embodiments, hemisalts of acids and bases are formed, for example, hemisulphate and hemicalcium salts.

**[0253]** Such pharmaceutically acceptable acid addition salts of compounds of Formula (I) or Formula (II) include, but are not limited to, a hydrobromide, hydrochloride, sulfate, nitrate, succinate, maleate, formate, acetate, adipate, besylate, bicarbonatecarbonate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, ethanedisulfonate, camphorsulfonate, chlorotheophyllonate, naphthalenesulfonate (e.g. 2-naphthalenesulfonate), hexanoate salt, bisulphatesulphate, borate, camsylate, cyclamate, edisylate, esylate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hippurate, hydrochloridechloride, hydrobromidebromide, hydroiodideiodide, isethionate, lactobionate, laurylsulphate, malate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, naphthylate, 2-napsylate, nicotinate, octadecanoate, oleate, orotate, oxalate, palmitate, pamoate, phosphatehydrogen phosphatedihydrogen phosphate, polygalacturonate, pyroglutamate, saccharate, stearate, sulfosalicylate, tannate, tosylate, trifluoroacetate and xinofoate salts.

**[0254]** The organic acid or inorganic acids used to form certain pharmaceutically acceptable acid addition salts of compounds of Formula (I) or Formula (II) include, but are not limited to, hydrobromic acid, hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, succinic acid, maleic acid, malonic acid, mandelic acid, formic acid, acetic acid, propionic acid, glycolic acid, oxalic acid, fumaric acid, citric acid, tartaric acid, lactic acid, benzoic acid, salicylic acid, glutamic acid, aspartic acid, toluenesulfonic acid, sulfosalicylic acid, benzenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, naphthalenesulfonic acid, such as 2-naphthalenesulfonic acid, or hexanoic acid.

**[0255]** Such pharmaceutically acceptable base addition salt of compounds of Formula (I) or Formula (II) include, but are not limited to, ammonium, aluminium, arginine, benzathine, calcium, choline, copper, diethylamine, diolamine, glycine, isopropylamine, choline, diethanolamine, piperazine, iron, lysine, magnesium, meglumine, olamine, potassium, silver, sodium, tromethamine and zinc salts.

**[0256]** The organic or inorganic bases used to form certain pharmaceutically acceptable base addition salt of compounds of Formula (I) or Formula (II) include, but are not limited to, salts derived from ammonium salts and metals from columns

Ito XII of the periodic table, or salts derived from primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like.

**[0257]** In certain embodiments, the free acid or free base forms of the compounds of Formula (I) or Formula (II) provided herein are prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound Formula (I) in an acid addition salt form is converted to the corresponding free base by treating with a suitable base (by way of example only, an ammonium hydroxide solution, a sodium hydroxide, and the like). For example, a compound of Formula (I) in a base addition salt form is converted to the corresponding free acid by treating with a suitable acid (by way of example only, hydrochloric acid).

**[0258]** Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

**[0259]** In certain embodiments, compounds of Formula (I) or Formula (II) in unoxidized form are prepared from N-oxides of compounds Formula (I) or Formula (II) by treating with a reducing agent (by way of example only, sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (by way of example only, acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80° C.

**[0260]** In certain embodiments, compounds of Formula (I) or Formula (II) are prepared as protected derivatives using methods known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry," 3<sup>rd</sup> edition, John Wiley and Sons, Inc., 1999.

**[0261]** In certain embodiments, compounds of Formula (I) or Formula (II) are prepared or formed, as solvates (e.g., hydrates). In certain embodiments, hydrates of compounds of Formula (I) or Formula (II) are prepared by recrystallization from an aqueousorganic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

**[0262]** Furthermore, the compounds of the present invention, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization. The compounds of the present invention may inherently or by design form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the invention embrace both solvated and unsolvated forms. The term "solvate" refers to a molecular complex of a compound of the present invention (including pharmaceutically acceptable salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like. The term "hydrate" refers to the complex where the solvent molecule is water.

**[0263]** The compounds of the present invention, including salts, hydrates and solvates thereof, may inherently or by design form polymorphs.

**[0264]** Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention can be present in racemic or enantiomerically enriched, for example the (R)-,

(S)- or (R,S)-configuration. In certain embodiments, each asymmetric atom has at least 50% enantiomeric excess, at least 60% enantiomeric excess, at least 70 enantiomeric excess, at least 80% enantiomeric excess, at least 90% enantiomeric excess, at least 95% enantiomeric excess, or at least 99% enantiomeric excess in the (R)- or (S)-configuration. Substituents at atoms with unsaturated double bonds may, if possible, be present in cis- (Z)- or trans- (E)- form.

**[0265]** Accordingly, as used herein a compound of the present invention can be in the form of one of the possible isomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (cis or trans) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

**[0266]** Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

**[0267]** Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, e.g., by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, e.g., by fractional crystallization of a salt formed with an optically active acid, e.g., tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-O,O'-p-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, e.g., high pressure liquid chromatography (HPLC) using a chiral adsorbent.

**[0268]** In certain embodiments, compounds of Formula (I) or Formula (II) are prepared as their individual stereoisomers. In other embodiments, the compounds of Formula (I) or Formula (II) provided herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In certain embodiments, resolution of enantiomers is carried out using covalent diastereomeric derivatives of the compounds of Formula (I) or Formula (II), or by using dissociable complexes (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubility, reactivity, etc.) and are readily separated by taking advantage of these dissimilarities. In certain embodiments, the diastereomers are separated by chromatography, or by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions," John Wiley And Sons, Inc., 1981.

**[0269]** Mixtures of isomers obtainable according to the invention can be separated in a manner known to those skilled in the art into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel or by e.g. medium

pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation, or by chromatography over optically active column materials.

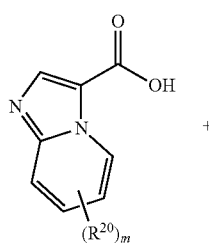
**[0270]** Depending on the choice of the starting materials and procedures, certain embodiments of the compounds of the present invention are present in the form of one of the possible isomers or as mixtures thereof, for example as pure optical isomers, or as isomer mixtures, such as racemates and diastereoisomer mixtures, depending on the number of asymmetric carbon atoms. The present invention is meant to include all such possible isomers, including racemic mixtures, diastereomeric mixtures and optically pure forms. Optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

**[0271]** Compounds of Formula (I) or Formula (II) are made by processes described herein and as illustrated in the Examples. Intermediates and final products can be worked up and/or purified according to standard methods, e.g. using chromatographic methods, distribution methods, (re-) crystallization, and the like. The invention relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in a protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ. All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents and catalysts utilized to synthesize the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art.

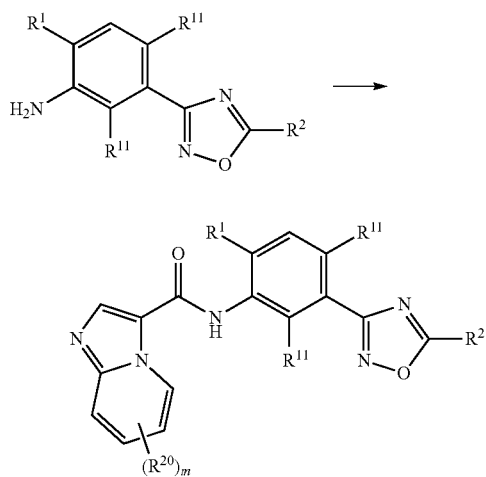
**[0272]** Non-limiting examples of synthetic schemes used to make compounds of the invention are illustrated in reaction schemes (I)-(IV). The R<sub>1</sub>, R<sub>20</sub>, R<sub>11</sub> and R<sub>2</sub> groups as defined herein.

**[0273]** Scheme (I) illustrates the synthesis of compounds of Formula (I) by coupling the amine with the carboxylic acid in the presence of a base and a coupling reagent. By way of example only, the coupling reagent is HATU and the base is diisopropylethylamine.

Scheme (I)

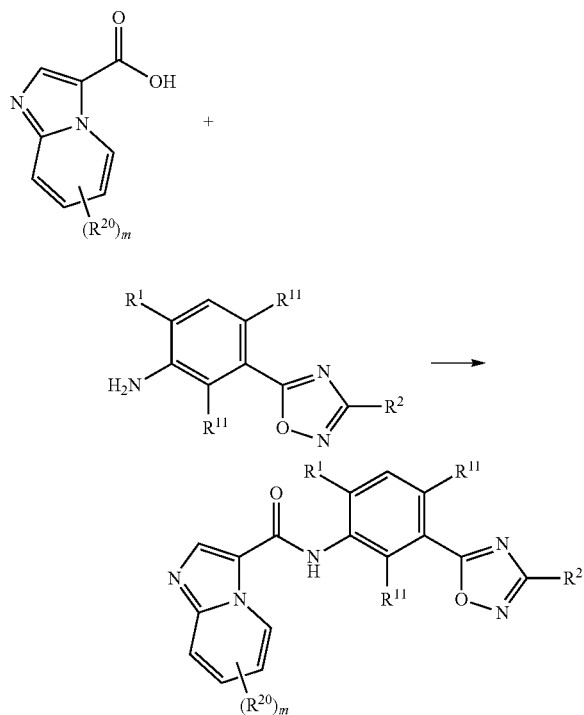


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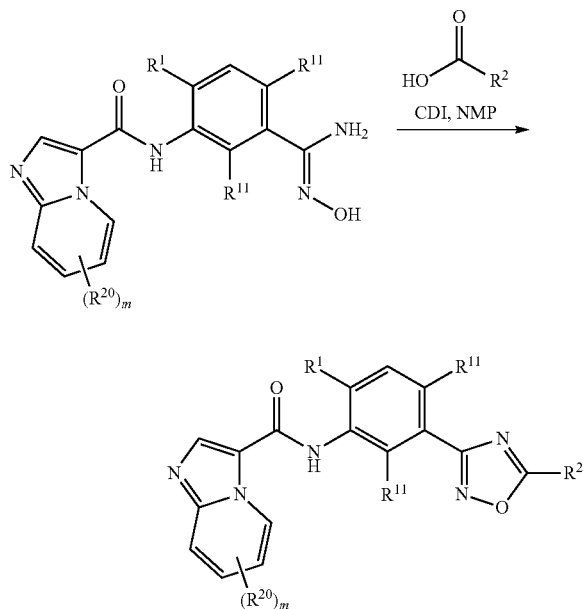
**[0274]** Scheme (II) illustrates the synthesis of compounds of Formula (II) by coupling the amine with the carboxylic acid in the presence of a base and a coupling reagent. By way of example only, the coupling reagent is HATU and the base is diisopropylethylamine.

Scheme (II)



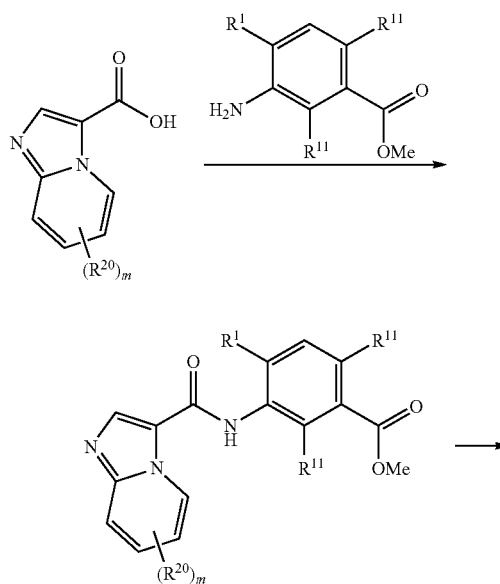
**[0275]** Scheme (III) illustrates the synthesis of compounds of Formula (I) by formation of the oxadiazole from the corresponding N'-hydroxyformimidamide and carboxylic acid.

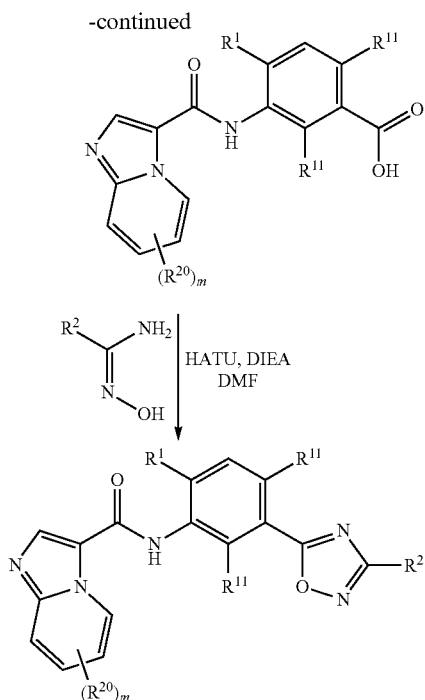
Scheme (III)



**[0276]** Scheme (IV) illustrates the synthesis of compounds of Formula (II) by formation of the oxadiazole from the corresponding N'-hydroxyformimidamide and carboxylic acid.

Scheme (IV)





[0277] The examples provided herein are offered to illustrate, but not to limit, the compounds of Formula (I) or Formula (II) provided herein, and the preparation of such compounds.

#### Pharmacology and Utility

[0278] Protein tyrosine kinases (PTK) play a central role in the regulation of a wide variety of cellular processes and maintaining control over cellular function. Protein kinases catalyze and regulate the process of phosphorylation, whereby the kinases covalently attach phosphate groups to proteins or lipid targets in response to a variety of extracellular signals. Examples of such stimuli include hormones, neurotransmitters, growth and differentiation factors, cell cycle events, environmental stresses and nutritional stresses. An extracellular stimulus may affect one or more cellular responses related to cell growth, migration, differentiation, secretion of hormones, activation of transcription factors, muscle contraction, glucose metabolism, control of protein synthesis, and regulation of the cell cycle.

[0279] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events. These diseases include, but are not limited to, autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, respiratory diseases, allergies and asthma, Alzheimer's disease, and hormone-related diseases.

[0280] Examples of protein-tyrosine kinases include, but are not limited to,

[0281] (a) tyrosine kinases such as Irk, IGFR-1, Zap-70, Bmx, Btk, CHK (Csk homologous kinase), CSK (C-terminal Src Kinase), Itk-1, Src (c-Src, Lyn, Fyn, Lck, Syk, Hck, Yes, Blk, Fgr and Frk), Tec, Txk/Rlk, Abl, EGFR (EGFR-1/ErbB-1, ErbB-2/NEUHER-2, ErbB-3 and ErbB-4), FAK, FGF1R (also FGFR1 or FGR-1), FGF2R

(also FGR-2), MET (also Met-I or c-MET), PDGFR ( $\alpha$  and  $\beta$ ), Tie-1, Tie-2 (also Tek-1 or Tek), VEGFR1 (also FLT-1), VEGFR2 (also KDR), FLT-3, FLT-4, c-KIT, JAK1, JAK2, JAK3, TYK2, LOK, RET, TRKA, PYK2, ALK (Anaplastic Lymphoma Kinase), EPHA (1-8), EPHB (1-6), RON, Fes, Fer or EPHB4 (also EPHB4-1), and

[0282] (b) and serine/threonine kinases such as Aurora, c-RAF, SGK, MAP kinases (e.g., MKK4, MKK6, etc.), SAPK2a, SAPK26, Ark, ATM (1-3), CamK (1-IV), CamKK, Chk1 and 2 (Checkpoint kinases), CK1, CK2, Erk, IKK-I (also IKK- $\alpha$  or CHUK), IKK-2 (also IKK- $\beta$ ), Ilk, Jnk (1-3), LimK (1 and 2), MLK3Raf (A, B, and C), CDK (1-10), PKC (including all PKC subtypes), Plk (1-3), NIK, Pak (1-3), PDK1, PKR, RhoK, RIP, RIP-2, GSK3 ( $\alpha$  and  $\beta$ ), PKA, P38, Erk (1-3), PKB (including all PKB subtypes) (also AKT-1, AKT-2, AKT-3 or AKT3-1), IRAK1, FRK, SGK, TAK1 and Tp1-2 (also COT).

[0283] Phosphorylation modulates or regulates a variety of cellular processes such as proliferation, growth, differentiation, metabolism, apoptosis, motility, transcription, translation and other signaling processes. Aberrant or excessive PTK activity has been observed in many disease states including, but not limited to, benign and malignant proliferative disorders, diseases resulting from inappropriate activation of the immune system and diseases resulting from inappropriate activation of the nervous systems. Specific diseases and disease conditions include, but are not limited to, autoimmune disorders, allograft rejection, graft vs. host disease, diabetic retinopathy, choroidal neovascularization due to age-related macular degeneration, psoriasis, arthritis, osteoarthritis, rheumatoid arthritis, synovial pannus invasion in arthritis, multiple sclerosis, myasthenia gravis, diabetes mellitus, diabetic angiopathy, retinopathy of prematurity, infantile hemangiomas, non-small cell lung, bladder and head and neck cancers, prostate cancer, breast cancer, ovarian cancer, gastric and pancreatic cancer, psoriasis, fibrosis, rheumatoid arthritis, atherosclerosis, restenosis, auto-immune disease, allergy, respiratory diseases, asthma, transplantation rejection, inflammation, thrombosis, retinal vessel proliferation, inflammatory bowel disease, Crohn's disease, ulcerative colitis, bone diseases, transplant or bone marrow transplant rejection, lupus, chronic pancreatitis, cachexia, septic shock, fibroproliferative and differentiative skin diseases or disorders, central nervous system diseases, neurodegenerative diseases, disorders or conditions related to nerve damage and axon degeneration subsequent to a brain or spinal cord injury, acute or chronic cancer, ocular diseases, viral infections, heart disease, lung or pulmonary diseases or kidney or renal diseases and bronchitis.

[0284] Tyrosine kinases can be broadly classified as receptor-type (having extracellular, transmembrane and intracellular domains) or the non-receptor type (being wholly intracellular) protein tyrosine kinases. Tyrosine kinases transfer the terminal phosphate of ATP to tyrosine residues of proteins thereby activating or inactivating signal transduction pathways. Inappropriate or uncontrolled activation of many of these kinase (aberrant protein tyrosine kinase activity), for example by over-expression or mutation, results in uncontrolled cell growth. Many of the protein tyrosine kinases, whether a receptor or non-receptor tyrosine kinase have been found to be involved in cellular signaling pathways involved

in numerous pathogenic conditions, including, but not limited to, immunomodulation, inflammation, or proliferative disorders such as cancer.

#### c-Kit

**[0285]** Mast cells are tissue elements derived from a particular subset of hematopoietic stem cells that express CD34, c-kit and CD13 antigens. Mast cells are characterized by their heterogeneity, not only regarding tissue location and structure but also at the functional and histochemical levels. Immature mast cell progenitors circulate in the bloodstream and differentiate into various tissues. These differentiation and proliferation processes are under the influence of cytokines, one of importance being Stem Cell Factor (SCF), also termed c-Kit ligand, Steel factor or Mast Cell Growth Factor. The Stem Cell Factor receptor is encoded by the protooncogene, c-kit, which is expressed in hematopoietic progenitor cells, mast cells, germ cells, interstitial cells of Cajal (ICC), and some human tumors, and is also expressed by non hematopoietic cells.

**[0286]** Stem cell factor (SCF), also known as c-kit ligand, is the primary regulating factor for human mast cell growth and function. The SCF receptor, c-kit receptor, is a Type III transmembrane receptor protein tyrosine kinase which initiates cell growth and proliferation signal transduction cascades in response to SCF binding. Ligation of c-kit receptor by SCF induces its dimerization followed by its transphosphorylation, leading to the recruitment and activation of various intracytoplasmic substrates. These activated substrates induce multiple intracellular signaling pathways responsible for cell proliferation and activation. These proteins are known to be involved in many cellular mechanisms, which in case of disruption, lead to disorders such as abnormal cell proliferation and migration, as well as inflammation.

**[0287]** The relationship between mast cells, SCF and c-kit receptor is discussed in the following references: Huang, E. et al., "The hematopoietic growth factor KL is encoded by the SI locus and is the ligand of the c-kit receptor, the gene product of the W locus", *Cell*, 63, 225-233, 1990; Zsebo, K. M. et al., "Stem cell factor is encoded at the SI locus of the mouse and is the ligand for the c-kit tyrosine kinase receptor", *Cell*, 63, 213-224, 1990; Zhang, S. et al., "Cytokine production by cell cultures from bronchial subepithelial myofibroblasts", *J. Pathol.*, 180, 95-10, 1996; Zhang, S. et al., "Human mast cells express stem cell factor", *J. Pathol.*, 186, 59-66, 1998; Kassel, O. et al., "Up and down-regulation by glucocorticoids of the constitutive expression of the mast cell growth factor stem cell factor by human lung fibroblasts in culture", *Mol. Pharmacol.*, 54, 1073-1079, 1998; Kassel, O. et al., "Human bronchial smooth muscle cells in culture produce Stem Cell Factor", *Eur. Respir. J.*, 13, 951-954, 1999; Kassel, O. et al., "The Stem Cell Factor, Stem cell factor, its Properties and Potential Role in the Airways", *Pulmonary Pharmacology & Therapeutics*, 14, 227-288, 2001; de Paulis, A. et al., "Stem cell factor is localized in, released from, and cleaved by human mast cells", *J. Immunol.*, 163, 2799-2808, 1999; Mol, C. D. et al., "Structure of a c-kit product complex reveals the basis for kinase transactivation", *J. Biol. Chem.*, 278, 31461-31464, 2003; Iemura, A. et al., "The c-kit ligand, stem cell factor, promotes mast cell survival by suppressing apoptosis", *Am. J. Pathol.*, 144, 321-328, 1994; Nilsson, G. et al., "Stem cell factor is a chemotactic factor for human mast cells", *J. Immunol.*, 153, 3717-3723, 1994; Meiningner, C. J. et al., "The c-kit receptor ligand functions as a mast cell chemoattractant",

*Blood*, 79, 958-963, 1992, and Klnashi, T. et al., "Steel factor and c-kit regulate cell-matrix adhesion", *Blood*, 83, 1033-1038, 1994.

**[0288]** The following references discuss the c-kit signaling pathway and its relationship with various downstream pathways and the relationship with diseases associated with mast cells: Thornmes, K. et al., "Identification of Tyr-703 and Tyr-936 as the primary association sites for Grb2 and Grb7 in the c-Kit/ste203 cell factor receptor", *Biochem.*, 341, 211-216, 1999; Ishizuka, T. et al., "Stem cell factor augments Fc epsilon RI-mediated TNF-alpha production and stimulates MAP kinases via a different pathway in MC9 mast cells", *J. Immunol.*, 161, 3624-3630, 1998; Timokhina, I. et al., "Kit signaling through PI 3-kinase and Src kinase pathways: an essential role for Rac1 and JNK activation in mast cell proliferation", *EMBO J.*, 17, 6250-6262, 1998; Tang, B. et al., "Tec kinase associates with c-kit and is tyrosine phosphorylated and activated following stem cell factor binding", *Mol. Cell. Biol.*, 14, 8432-8437, 1994, and Ueda, S. et al., "Critical roles of c-Kit tyrosine residues 567 and 719 in stem cell factor-induced chemotaxis: contribution of src family kinase and PI3-kinase on calcium mobilization and cell migration", *Blood*, 99, 3342-3349, 2002.

**[0289]** Mast cells are the primary effector cells in allergic inflammation. Mast cells are also involved in other pathogenic processes such as acute inflammation and fibrosis. Mast cells present in tissues of patients are implicated in or contribute to the genesis of diseases such as autoimmune diseases (multiple sclerosis, rheumatoid arthritis, inflammatory bowel diseases (IBD)), allergic diseases (allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing vasculitis and insect bite skin inflammation and bronchial asthma), tumor angiogenesis, germ cell tumors, mast cell tumors, gastrointestinal stromal tumors, small-cell lung cancer, melanoma, breast cancer, acute myelogenous leukemia, glioblastoma, neuroblastoma and mastocytosis, inflammatory diseases, diabetes, type I diabetes, type II diabetes, irritable bowel syndrome (IBS), CNS disorders and interstitial cystitis. In these diseases, mast cells participate in the destruction of tissues by releasing a cocktail of different proteases and mediators categorized into three groups: preformed granule-associated mediators (histamine, proteoglycans, and neutral proteases), lipid-derived mediators (prostaglandins, thromboxanes and leukotrienes), and various cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, TNF- $\alpha$ , GM-CSF, MIP-1 $\alpha$ , MIP-1 $\beta$ , MIP-2 and IFN- $\gamma$ ). The liberation by activated mast cells of mediators (TNF- $\alpha$ , histamine, leukotrienes, prostaglandins etc.) as well as proteases may i) induce inflammation and vasodilatation and ii) participate in the tissue destruction process.

**[0290]** In addition, mast cell activation induces diverse effector responses, such as secretion of allergic mediators, proteases, chemokines such as MCP-1 and RANTES, leukotrienes, prostaglandins and neurotrophins; and induction of cytokine gene transcription (IL-4, IL-5, IL-6, IL-13, TNF- $\alpha$  and GM-CSF). These mediators contribute to creating the asthmatic phenotype by their effects on endothelial cells, smooth muscle cells and fibroblasts and on extracellular matrix, and by recruiting other inflammatory cells.

**[0291]** Asthma is characterized by airflow obstruction, bronchial hyper responsiveness and airway inflammation. Airway inflammation is the major factor in the development

and perpetuation of asthma. In allergic asthma, allergens are thought to initiate the inflammatory process by inducing a T-lymphocyte mediated response (TH2) that results in the production of allergen-specific IgE. IgE binds to its high-affinity receptor FcεRI on pulmonary mast cells, triggering a type I (IgE-mediated) immediate allergic response. Thus, mast cells play a role in asthma.

**[0292]** The activation of mast cells by different stimuli such as stress, trauma, infection and neurotransmitters, also participate in the exacerbation of the chemical imbalance causing CNS disorders. More specifically, mast cell degranulation is stimulated by common neurotransmitters such as neurotensin, somatostatin, substance P and acetylcholine, by growth or survival factors, notably such as NGF. Mast cells involved in the response to such stimulus can be brain mast cells but also other mast cells releasing the content of their granules in the blood stream that ultimately reach sensory, motor or brain neurons. Following mast cells activation, released granules liberate various factors capable of modulating and altering neurotransmission and neurons survival. Among such factors, serotonin is important since an increase of the level of free serotonin has been observed in depressed patients. Alternatively, the sudden burst of serotonin may be followed by a period of serotonin shortage, leading to pain and migraine. As a consequence, it is believed that mast cells exacerbate in autocrine or paracrine manner the deregulation of neurotransmission. For example, anxiety or stress-induced release of neurotransmitters such as serotonin activates mast cells, which in turn release the content of their granules, further contributing to the chemical imbalance in the brain leading to CNS disorders.

**[0293]** Other mediators released by mast cells can be categorized into vasoactive, nociceptive, proinflammatory and other neurotransmitters. Taken together, these factors are able to induce disturbance in the activity of neurons, whether they are sensory, motor, or CNS neurons. In addition, patients afflicted with mastocytosis are more inclined to develop CNS disorders than the normal population. This can be explained by the presence of activating mutations in the c-kit receptor, which induce degranulation of mast cells and a burst of factors contributing to chemical imbalance and neurotransmission alteration.

**[0294]** The activation of mast cells by different drugs, including, but not limited to, salicylic derivatives, morphine derivatives, opioids, heroin, amphetamines, alcohol, nicotine, analgesics, anesthetics, and anxiolytics results in the degranulation of mast cells, which participate in the exacerbation of the chemical imbalance responsible for drug habituation and withdrawal syndrome. Following mast cells activation, released granules liberate various factors capable of modulating and altering neurotransmission. Among such factors is morphine which is bound or stored in mast cells granules. Tobacco smoke also induces the release of mediators from canine mast cells and modulates prostaglandin production leading to asthma. In addition, patients afflicted with mastocytosis are more inclined to develop substance use disorders than the normal population. This can be explained by the presence of activating mutations in the c-kit receptor, which induce degranulation of mast cells and a burst of factors contributing to chemical imbalance and neurotransmission alteration.

**[0295]** Mast cells have also been identified to be involved in or to contribute to drug dependence and withdrawal symptoms.

**[0296]** The relationship between mast cells, SCE and c-kit kinase in various diseases is discussed in the following references: Oliveira et al., "Stem Cell Factor: A Hemopoietic Cytokine with Important Targets in Asthma", *Current Drug Targets*, 2: 313-318, 2003; Puxeddu et al., "Mast cells in allergy and beyond", *The International Journal of Biochemistry & Cell Biology*, 35: 1601-1607, 2003; Rottem et al., "Mast cells and autoimmunity", *Autoimmunity Reviews*, 4: 21-27, 2005; Woolley, D. E. et al., "The mast cell in inflammatory arthritis", *N. Engl. J. Med.*, 348:1709-1711, 2003; Benoist, C. et al., "Mast cells in autoimmune disease", *Nature*, 420:875-878, 2002; Nigrovic, P. A. et al., "Mast cells in inflammatory arthritis", *Arthritis Res. Ther.*, 7:1-11, 2005; Wang, H. W. et al., "Mast cell accumulation and cytokine expression in the tight skin mouse model of scleroderma", *Exp. Dermatol.*, 14, 295-302, 2005; Olsson, N. et al., "Demonstration of mast cell chemotactic activity in bronchoalveolar lavage fluid collected from asthmatic patients before and during pollen season", *J. Allergy Clin. Immunol.*, 105,455-461, 2000; Ma, Y. et al., "Indolinone derivatives inhibit constitutively activated Kit mutants and kill neoplastic mast cells", *J. Invest. Dermatol.*, 114, 392-394, 2000; Kobayashi, Y. et al., "Mst Cells as a Target of Rheumatoid Arthritis Treatment", *Jon. J. Pharmacol.*, 7-11, 2002, and Ai-Muhsen, S. Z. et al., "The expression of stem cell factor and c-kit receptor in human asthmatic airways", *Clin. Exp. Allergy*, 34, 911-916, 2004.

**[0297]** In addition, the treatment of asthma and arthritis with administration of c-kit inhibitor is presented in the following references: Takeuchi et al., "STI571 inhibits growth and adhesion of human mast cells in culture", *Journal of Leukocyte Biology*, 74: 1026-1034, 2003; Berlin et al., "Treatment of Cockroach Allergen Asthma Model with imatinib Attenuates Airway Responses", *American Journal of Respiratory and Critical care Medicine*, 171: 35-39, 2005; Ekland et al., "Treatment of rheumatoid arthritis with imatinib mesylate: clinical improvement in three refractory cases", *Annals of Medicine*, 35: 362-367, 2003; Miyachi et al., "Efficacy of imatinib mesylate (STI571) treatment for a patient with rheumatoid arthritis developing chronic myelogenous leukemia", *Clinical Rheumatology*, 22: 329-332, 2003; Juurikivi et al., "Inhibition of c-kit tyrosine kinase by imatinib mesylate induces apoptosis in mast cells in rheumatoid synovial: a potential approach to the treatment of arthritis", *Ann. Rheum. Dis.*, 64: 1126-1131, 2005; Wolf, A. M., et al., "The kinase inhibitor imatinib mesylate inhibits TNF-alpha production in vitro and prevents TNF-dependent acute hepatic inflammation", *Proc. Natl. Acad. Sci. U. S. A.* 102:13622-13627, 2005; Leath et al., "Novel and emerging therapies for asthma", *Drug Discovery Today*, 10(2324): 1647-1655, 2005; Berlin et al., "Inhibition of SCF attenuates peribronchial remodeling in chronic cockroach allergen-induced asthma", *Laboratory Investigations*, 86: 557-565, 2006; Paniagua et al., "Selective tyrosine kinase inhibition by imatinib mesylate for the treatment of autoimmune arthritis", *The Journal of Clinical Investigation*, 116(10): 2633-2642, 2006; Wenzel et al., "Update in Asthma", *American Journal of Respiratory and Critical care Medicine*, 173: 698-706, 2006; Chaudhary et al., "Pharmacological Differentiation of Inflammation and Fibrosis in the Bleomycin Model", *American Journal of Respiratory and Critical care Medicine*, 173: 769-776, 2006, and Reber et al., "Review: Stem cell factor and its receptor c-Kit as targets for inflammatory diseases", *European Journal of Pharmacology*, 533: 327-340, 2006.

**[0298]** The activity of the c-kit receptor is regulated in normal cells, and the normal functional activity of this c-kit gene product is important for the maintenance of normal hematopoiesis, melanogenesis, genitogenesis, and growth and differentiation of mast cells. Inhibition of c-kit kinase activity reduces the growth and differentiation of mast cells and thereby mediates the diseases and/or conditions associated with mast cells, such as autoimmune diseases, multiple sclerosis, rheumatoid arthritis, inflammatory bowel diseases (IBD), respiratory diseases, allergic diseases, allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing vasculitis and insect bite skin inflammation, bronchial asthma, tumor angiogenesis, germ cell tumors, mast cell tumors, gastrointestinal stromal tumors, small-cell lung cancer, melanoma, breast cancer, acute myelogenous leukemia, glioblastoma, neuroblastoma and mastocytosis, inflammatory diseases, diabetes, type I diabetes, type II diabetes, irritable bowel syndrome (IBS), CNS disorders and interstitial cystitis

**[0299]** In addition to its importance in normal cellular physiologic activities, c-kit kinase plays a role in the biological aspects of certain human cancers, and unregulated c-kit kinase activity is implicated in the pathogenesis of human cancers, and in certain tumors types. Proliferation of tumor cell growth mediated by c-kit can occur by a specific mutation of the c-kit polypeptide that results in ligand independent activation or by autocrine stimulation of the receptor. In the former case, mutations that cause constitutive activation of c-kit kinase activity in the absence of SCF binding are implicated in malignant human cancers, including germ cell tumors, mast cell tumors, gastrointestinal stromal tumors, small-cell lung cancer, melanoma, breast cancer, acute myelogenous leukemia, glioblastoma, neuroblastoma and mastocytosis.

**[0300]** A proliferation assay for the evaluation of the efficacy of c-kit inhibitors and PDGFR inhibitors is given in Kuriu et al., "Proliferation of human myeloid leukemia cell line associated with the tyrosine-phosphorylation and activation of the proto-oncogene c-kit product", *Blood*, 78(II): 2834-2840, 1991; Heinrich et al., "Inhibition of c-kit receptor tyrosine kinase activity by STI571, a selective tyrosine kinase inhibitor", *Blood*, 96(3): 925-932, 2000; Buchdunger et al., "Abl Protein-Tyrosine Kinase Inhibitor STI571 Inhibits In Vitro Signal Transduction Mediated by c-Kit and Platelet-Derived Growth Factor Receptors", *The Journal of Pharmacology and Experimental Therapeutics*, 295(1): 139-145, 2000; and Smolich et al., "The antiangiogenic protein kinase inhibitors SU5416 and SU6668 inhibit the SCE receptor (c-kit) in a human myeloid leukemia cell line and in acute myeloid leukemia blasts", *Blood*, 97(5): 1413-1421, 2001. This assay use MO7e cells, which are a human promegakaryocytic leukemia cell line that depend on SCF for proliferation. These references in combination with Berlin et al., Ekland et al., and Miyachi et al., (cited above) show that that a c-kit kinase inhibitor screened via this proliferation assay was later found to treat rheumatoid arthritis and asthma.

**[0301]** In addition, a compound that was initially evaluated for its efficacy as a c-kit inhibitor using a proliferation assay based on Ba/F3 cells and Ba/F3-derived cells (see WO 2004/01903) was later found to be effective in the treatment of mast cell tumours and asthma (see Bellamy F. et al., "Pharmacokinetics of masitinib in cats", *Vet. Res. Commun.*, June 16

(epub) 2009; Hahn K. A. et al., "Masitinib is safe and effective for treatment of canine mast cell tumours", *J. Vet. Intern. Med.*, 22, 1301-1309, 2008 and Humbert M. et al. "Masitinib, a c-kit/PDGFR receptor tyrosine kinase inhibitor, improves disease control in severe corticosteroid-dependent asthmatics", *Am. J. Respir. Crit. Care Med.*, 179, 1194-1201, 2009.

**[0302]** c-kit receptor has a substantial homology to the PDGF receptor and to the CSF-1 receptor (c-Fms).

#### Platelet-derived Growth Factor (PDGF) Receptor Family

**[0303]** PDGF (Platelet-derived Growth Factor) is commonly occurring growth factor which plays an important role both in normal growth and in pathological cell proliferation. By way of example, such as that observed in carcinogenesis and in diseases of the smooth-muscle cells of blood vessels, for example in atherosclerosis and thrombosis. The PDGF growth factor family consists of PDGF-A, PDGF-B, PDGF-C and PDGF-D, which form either homo- or heterodimers (AA, AB, BB, CC, DD) that bind to the protein tyrosine kinase receptors PDGFR- $\alpha$  and PDGFR- $\beta$ . Dimerization of the growth factors is a prerequisite for activation of the kinase, as the monomeric forms are inactive. The two receptor isoforms dimerize upon binding resulting in three possible receptor combinations, PDGFR- $\alpha\alpha$ , PDGFR- $\beta\beta$  and PDGFR- $\alpha\beta$ . Growth factor AA binds only to - $\alpha\alpha$ , growth factor BB can bind with - $\alpha\alpha$ , - $\beta\beta$  and - $\alpha\beta$ , growth factors CC and AB specifically interact with - $\alpha\alpha$  and - $\alpha\beta$ , and growth factor DD binds to - $\beta\beta$ . The PDGF-receptor plays an important role in the maintenance, growth and development of hematopoietic and non-hematopoietic cells.

**[0304]** Key downstream mediators of PDGFR signaling are Ras/mitogen-activated protein kinase (MAPK), PI-3 kinase and phospholipase- $\gamma$  (PLC $\gamma$ ) pathways. MAPK family members regulate various biological functions by phosphorylation of target molecules (transcription factors and other kinases) and thus contribute to regulation of cellular processes such as proliferation, differentiation, apoptosis and immunoresponses. PI-3 kinase activation generated PIP3 which functions as a second messenger to activate downstream tyrosine kinases Btk and Itk, the Ser/Thr kinases PDK1 and Akt (PKB). Akt activation is involved in survival, proliferation and cell growth. After activation PLC hydrolyses its substrate, PtdIns(4,5)P2, and forms two secondary messengers, diacylglycerol and Ins(1,4,5)P3 which stimulates intracellular processes such as proliferation, angiogenesis and cell motility.

**[0305]** PDGFR is expressed on early stem cells, mast cells, myeloid cells, mesenchymal cells and smooth muscle cells. Only PDGFR-p is implicated in myeloid leukemias-usually as a translocation partner with Tel, Huntingtin interacting protein (HIP1) or Rabaptin5. Activation mutations in PDGFR- $\alpha$  kinase domain are associated with gastrointestinal stromal tumors (GIST).

**[0306]** Certain embodiments of compounds of Formula (I) and Formula (II) provided herein inhibit PDGF receptor (PDGFR $\alpha$  and PDGFR $\beta$ ) activity and c-kit kinase activity, and are useful for the treatment of diseases, which respond to an inhibition of the PDGF receptor kinase. Therefore, certain compounds of Formula (I) and Formula (II) provided herein are useful for the treatment of tumor diseases, such as gliomas, sarcomas, prostate tumors, small cell lung cancer and tumors of the colon, breast, and ovary. In addition certain embodiments of compounds of Formula (I) and Formula (II) provided herein are useful to treat disorders, such as thrombosis, psoriasis, scleroderma, fibrosis, asthma, metabolic dis-



eases and hypereosinophilia. Compounds of Formula (I) and Formula (II) provided herein are also effective against diseases associated with vascular smooth-muscle cell migration and proliferation, such as restenosis and atherosclerosis.

**[0307]** Patients with obliterative bronchiolitis (OB), a chronic rejection of allogenic lung transplants, often show an elevated PDGF concentration in bronchoalveolar lavage fluids. In certain embodiments, compounds of Formula (I) and Formula (II) provided herein exhibit useful effects in the treatment of disorders arising as a result of transplantation, for example, allogenic transplantation, especially tissue rejection, such as obliterative bronchiolitis (OB).

**[0308]** In certain embodiments, compounds of Formula (I) and Formula (II) provided herein are useful for the protection of stem cells, for example to combat the hemotoxic effect of chemotherapeutic agents, such as 5-fluorouracil.

**[0309]** The compounds of Formula (I) and Formula (II) provided herein, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are inhibitors of c-kit kinase activity or are inhibitors of c-kit kinase activity and PDGFR ( $\alpha$  and  $\beta$ ) kinase activity. In certain embodiments, the compounds of Formula (I) and Formula (II) provided herein, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are inhibitors of c-kit kinase activity and PDGFR ( $\alpha$  and  $\beta$ ) kinase activity. In other embodiments, the compounds of Formula (I) and Formula (II) provided herein, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are inhibitors of either c-kit kinase activity. Such compounds of Formula (I) and Formula (II) provided herein, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are useful for treating diseases or disorders in which c-kit kinase, or c-kit and PDGFR ( $\alpha$  and/or  $\beta$ ) kinase, contributes to the pathology and/or symptomatology of a disease or disorder. Such diseases or disorders include, but are not limited to, a mast cell associated disease, inflammatory diseases, respiratory diseases, an allergy disorder, fibrosis diseases, metabolic diseases, autoimmune diseases, a CNS related disorder, a neurodegenerative disorder, neurological diseases, dermatological diseases, a graft-versus-host disease, a pain condition, a neoplastic disorder, a cardiovascular disease and cancer.

**[0310]** Non-limiting examples of such diseases include asthma, allergic rhinitis, allergic sinusitis, bronchial asthma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), pulmonary arterial hypertension (PAH), idiopathic arterial hypertension (IPAH), primary pulmonary hypertension (PPH), pulmonary fibrosis, liver fibrosis, cardiac fibrosis, scleroderma, urticaria, dermatoses, atopic dermatitis, allergic contact dermatitis, diabetes, type I diabetes, type II diabetes, rheumatoid arthritis, multiple sclerosis, cytopenias (by way of example only, anemia, leucopenia, neutropenia, thrombocytopenia, granulocytopenia, pancytopenia and idiopathic thrombocytopenic purpura), systemic lupus erythematosus, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohns disease, psoriasis, lymphomas (by way of example

only, B and T cell lymphomas), myelodysplastic syndrome, breast cancer, pancreatic cancer, papillary thyroid carcinoma, ovarian carcinoma, human adenoid cystic carcinoma, non small cell lung cancer, secretory breast carcinoma, congenital fibrosarcoma, congenital mesoblastic nephroma, acute myelogenous leukemia, chronic myeloid leukemia metastasis, cancer-related pain, neuroblastoma, osteosarcoma, melanoma, bone metastases, a tumor of breast, renal, lung, prostate, pancreas, colon, ovary, thyroid, colorectal tumors, neuronal tumors, uterine tumors, gastrointestinal stromal tumors (GIST), gliomas, sarcomas, tumor angiogenesis, germ cell tumors, mast cell tumors, glioblastoma, neuroblastoma, mastocytosis, osteoporosis, hypereosinophilia, restenosis, atherosclerosis, anaphylactic syndrome, angioedema, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis, insect bite skin inflammation, CNS disorders and interstitial cystitis.

**[0311]** In certain embodiments, the compounds of Formula (I) and Formula (II) provided herein, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are useful for treating diseases or disorders in which c-kit kinase contributes to the pathology and/or symptomatology of a disease or disorder. Non-limiting examples of such diseases include asthma, allergic rhinitis, allergic sinusitis, bronchial asthma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), pulmonary arterial hypertension (PAH), pulmonary fibrosis, liver fibrosis, cardiac fibrosis, scleroderma, urticaria, dermatoses, atopic dermatitis, allergic contact dermatitis, diabetes, type I diabetes, type II diabetes, rheumatoid arthritis, multiple sclerosis, cytopenias (by way of example only, anemia, leucopenia, neutropenia, thrombocytopenia, granulocytopenia, pancytopenia and idiopathic thrombocytopenic purpura), systemic lupus erythematosus, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohns disease, psoriasis, lymphomas (by way of example only, B and T cell lymphomas), myelodysplastic syndrome, breast cancer, pancreatic cancer, papillary thyroid carcinoma, ovarian carcinoma, human adenoid cystic carcinoma, non small cell lung cancer, secretory breast carcinoma, congenital fibrosarcoma, congenital mesoblastic nephroma, acute myelogenous leukemia, chronic myeloid leukemia metastasis, cancer-related pain, neuroblastoma, osteosarcoma, melanoma, bone metastases, a tumor of breast, renal, lung, prostate, pancreas, colon, ovary, thyroid, colorectal tumors, neuronal tumors, uterine tumors, gastrointestinal stromal tumors (GIST), gliomas, sarcomas, tumor angiogenesis, germ cell tumors, mast cell tumors, glioblastoma, neuroblastoma, mastocytosis, osteoporosis, hypereosinophilia, restenosis, atherosclerosis, anaphylactic syndrome, angioedema, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis, insect bite skin inflammation, CNS disorders and interstitial cystitis.

**[0312]** In certain embodiments, the compounds of Formula (I) and Formula (II) provided herein, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are useful for treating diseases or disorders in which c-kit kinase and PDGFR (a and/or p) kinase contribute to the pathology and/or symptomatology of a disease or disorder. Non-limiting examples of such diseases include asthma, allergic rhinitis, allergic sinusitis, bronchial asthma, irritable bowel syndrome

(IBS), inflammatory bowel disease (IBD), pulmonary arterial hypertension (PAH), pulmonary fibrosis, liver fibrosis, cardiac fibrosis, scleroderma, urticaria, dermatoses, atopic dermatitis, allergic contact dermatitis, diabetes, type I diabetes, type II diabetes, rheumatoid arthritis, multiple sclerosis, cytopenias (by way of example only, anemia, leucopenia, neutropenia, thrombocytopenia, granulocytopenia, pancytopenia and idiopathic thrombocytopenic purpura), systemic lupus erythematosus, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohns disease, psoriasis, lymphomas (by way of example only, B and T cell lymphomas), myelodysplastic syndrome, breast cancer, pancreatic cancer, papillary thyroid carcinoma, ovarian carcinoma, human adenoid cystic carcinoma, non small cell lung cancer, secretory breast carcinoma, congenital fibrosarcoma, congenital mesoblastic nephroma, acute myelogenous leukemia, chronic myeloid leukemia metastasis, cancer-related pain, neuroblastoma, osteosarcoma, melanoma, bone metastases, a tumor of breast, renal, lung, prostate, pancreas, colon, ovary, thyroid, colorectal tumors, neuronal tumors, uterine tumors, gastrointestinal stromal tumors (GIST), gliomas, sarcomas, tumor angiogenesis, germ cell tumors, mast cell tumors, glioblastoma, neuroblastoma, mastocytosis, osteoporosis, hypereosinophilia, restenosis, atherosclerosis, anaphylactic syndrome, angioedema, erythema nodosum, erythema multiforme, cutaneous necrotizing vasculitis, insect bite skin inflammation, CNS disorders and interstitial cystitis.

**[0313]** Another aspect provided herein includes methods for treating a cell-proliferative disease, comprising administering to a system or subject in need of such treatment an effective amount of a compound of Formula (I) and Formula (II), or pharmaceutically acceptable salts or pharmaceutical compositions thereof; wherein the cell-proliferative disease is lymphoma, osteosarcoma, melanoma, or a tumor of breast, renal, prostate, colorectal, thyroid, ovarian, pancreatic, neuronal, lung, uterine or gastrointestinal tumor.

**[0314]** In certain embodiments, the compounds of Formula (I) and Formula (II), pharmaceutically acceptable salts, solvates, N-oxides and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of diseases and/or disorders including, but not limited to, asthma, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, exercise-induced asthma, drug-induced asthma (including aspirin and NSAID-induced) and dust-induced asthma, chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus.

**[0315]** In certain embodiments, the compounds of Formula (I) and Formula (II), pharmaceutically acceptable salts, solvates, N-oxides and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of dermatological disorders including, but not limited to, psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrheic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, basal cell carcinoma, actinic keratosis, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions.

**[0316]** In certain embodiments, the compounds of Formula (I) and Formula (II), pharmaceutically acceptable salts, solvates, N-oxides and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of rheumatoid arthritis, irritable bowel syndrome, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis, Crohns disease, inflammatory bowel disease (IBD), Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome and Sazary syndrome.

**[0317]** In certain embodiments, the compounds of Formula (I) and Formula (II), pharmaceutically acceptable salts, solvates, N-oxides and isomers thereof, and pharmaceutical compositions provided herein are used in the treatment of cancer including, but not limited to, prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumor recurrences, and paraneoplastic syndromes.

**[0318]** Provided herein are compounds of Formula (I) and Formula (II), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II), or pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers or mixture of isomers thereof, for use in activating c-kit kinase activity, or c-kit kinase and PDGFR ( $\alpha$  and/or  $\beta$ ) kinase activity, and thereby are used to in the prevention or treatment of diseases and/or disorders associated with c-kit kinase activity, or c-kit kinase and PDGFR ( $\alpha$  and/or  $\beta$ ) kinase activity.

**[0319]** Also provided herein are methods for the treatment of a subject suffering from a disease and/or disorder associated with c-kit kinase activity, wherein the method includes administering to the subject in need thereof, an effective amount of a compound of Formula (I) or Formula (II), or pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, pro-

tected derivatives, individual isomers or mixture of isomers thereof, either alone or as part of a pharmaceutical composition as described herein.

**[0320]** Also provided herein are methods for the treatment of a subject suffering from a disease and/or disorder associated with c-kit kinase activity and PDGFR (a and/or p) kinase activity, wherein the method includes administering to the subject in need thereof, an effective amount of a compound of Formula (I) or Formula (II), or pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers or mixture of isomers thereof, either alone or as part of a pharmaceutical composition as described herein.

**[0321]** Provided herein is the use of a compound of Formula (I) or Formula (II), or pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers or mixture of isomers thereof, in the manufacture of a medicament for the treatment of a disease or disorder associated with c-kit kinase activity. Also provided herein is the use of a compound of Formula (I) or Formula (II), or pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers or mixture of isomers thereof, in the manufacture of a medicament for the treatment of a disease or disorder associated with c-kit kinase activity and PDGFR ( $\alpha$  and/or  $\beta$ ) kinase activity.

**[0322]** Furthermore, provided herein is the use of a compound having Formula (I) or Formula (II), or pharmaceutically acceptable salts or pharmaceutical compositions thereof, and optionally in combination with a therapeutically effective amount of a second agent, in the manufacture of a medicament for treating a disease or condition modulated by kinase activity, particularly c-kit, or c-kit and PDGFR ( $\alpha$  and  $\beta$ ).

**[0323]** In accordance with the foregoing, the present invention further provides a method for preventing or treating any of the diseases or disorders described above in a subject in need of such treatment, which method comprises administering to said subject a therapeutically effective amount of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof. For any of the above uses, the required dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired. (See, "Administration and Pharmaceutical Compositions," *infra*).

#### Administration and Pharmaceutical Compositions

**[0324]** For the therapeutic uses of compounds of Formula (I) and Formula (II), or pharmaceutically acceptable salts, solvates, N-oxides or isomers thereof, described herein, such compounds are administered in therapeutically effective amounts either alone or as part of a pharmaceutical composition. Accordingly, provided herein are pharmaceutical compositions, which comprise at least one compound of Formula (I) or Formula (II), or pharmaceutically acceptable salts solvates, N-oxides or isomers thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. In addition, such compounds and compositions are administered singly or in combination with one or more additional therapeutic agents. The method of administration of such compounds and compositions include, but are not limited to, oral administration, rectal administration, transdermal administration, parenteral, intravenous administration, intravitreal

administration, intramuscular administration, pulmonary administration, inhalation administration, intranasal administration, topical administration, ophthalmic administration or otic administration. In certain embodiments the method of administration of such compounds and compositions is oral administration. In other embodiments the method of administration of such compounds and compositions is pulmonary administration, inhalation administration or intranasal administration.

**[0325]** The therapeutically effective amount will vary depending on, among others, the disease indicated, the severity of the disease, the age and relative health of the subject, the potency of the compound administered, the mode of administration and the treatment desired. In certain embodiments, the daily dosage of a compound of Formula (I) and Formula (II), satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5 mg/kg per body weight. In certain embodiments, the daily dosage of a compound of Formula (I) and Formula (II), administered by inhalation, is in the range from 0.05 micrograms per kilogram body weight ( $\mu\text{g}/\text{kg}$ ) to 100 micrograms per kilogram body weight ( $\mu\text{g}/\text{kg}$ ). In other embodiments, the daily dosage of a compound of Formula (I) and Formula (II), administered orally, is in the range from 0.01 micrograms per kilogram body weight ( $\mu\text{g}/\text{kg}$ ) to 100 milligrams per kilogram body weight ( $\text{mg}/\text{kg}$ ). An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to about 100 mg of a compound of Formula (I) and Formula (II), conveniently administered, e.g. in divided doses up to four times a day or in controlled release form. In certain embodiment, unit dosage forms for oral administration comprise from about 1 to 50 mg of a compound of Formula (I) and Formula (II).

**[0326]** Other aspects provided herein are processes for the preparation of pharmaceutical composition which comprise at least one compound of Formula (I) or Formula (II), or pharmaceutically acceptable salts, solvates, N-oxides or isomers thereof. In certain embodiments, such processes include admixing a compound of the Formula (I) or Formula (II), or pharmaceutically acceptable salts, solvates, N-oxides or isomers thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients. In certain embodiments, the pharmaceutical compositions comprising a compound of Formula (I) or Formula (II) in free form, or in a pharmaceutically acceptable salt, solvate, N-oxide or isomeric form, in association with at least one pharmaceutically acceptable carrier, diluent or excipient are manufactured by mixing, granulating and/or coating methods. In other embodiments, such compositions optionally contain excipients, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In other embodiments, such compositions are sterilized.

**[0327]** In certain embodiments, the pharmaceutical compositions comprising at least one compound of Formula (I) or Formula (II) are adapted for oral administration for the treatment of diseases and/or disorders associated with c-kit kinase activity. In other embodiments, the pharmaceutical compositions comprising at least one compound of Formula (I) or Formula (II) are adapted for oral administration for the treatment of diseases and/or disorders associated with c-kit kinase and PDGFR (a and/or p) kinase activity.

**[0328]** In certain embodiments, the pharmaceutical compositions comprising at least one compound of Formula (I) or

Formula (II) are adapted for inhalation administration, including pulmonary administration, inhalation administration or intranasal administration, for the treatment of diseases and/or disorders associated with c-kit kinase activity. In other embodiments, the pharmaceutical compositions comprising at least one compound of Formula (I) or Formula (II) are adapted for inhalation administration, including pulmonary administration, inhalation administration or intranasal administration, for the treatment of diseases and/or disorders associated with c-kit kinase and PDGFR ( $\alpha$  and/or  $\beta$ ) kinase activity.

**[0329]** In certain embodiments, the pharmaceutical compositions comprising at least one compound of Formula (I) or Formula (II) are adapted for inhalation administration, including pulmonary administration, inhalation administration or intranasal administration, for the treatment of respiratory diseases with c-kit kinase activity. In certain embodiments, the respiratory disease is allergic rhinitis or asthma. In other embodiments, the pharmaceutical compositions comprising at least one compound of Formula (I) or Formula (II) are adapted for inhalation administration, including pulmonary administration, inhalation administration or intranasal administration, for the treatment of respiratory diseases associated with c-kit kinase and PDGFR (a and/or p) kinase activity.

**[0330]** In certain embodiments, the respiratory disease is allergic rhinitis or asthma. In certain embodiments, the pharmaceutical compositions comprising at least one compound of Formula (I) or Formula (II) are adapted for parenteral or intravenous administration, for the treatment of diseases and/or disorders associated with c-kit kinase activity. In other embodiments, the pharmaceutical compositions comprising at least one compound of Formula (I) or Formula (II) are adapted for parenteral or intravenous administration, for the treatment of diseases and/or disorders associated with c-kit kinase and PDGFR (a and/or p) kinase activity.

#### Oral Dosage Forms

**[0331]** In certain embodiments, the pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II) are administered orally as discrete dosage forms, wherein such dosage forms include, but are not limited to, capsules, gelatin capsules, caplets, tablets, chewable tablets, powders, granules, syrups, flavored syrups, solutions or suspensions in aqueous or non-aqueous liquids, edible foams or whips, and oil-in-water liquid emulsions or water-in-oil liquid emulsions.

**[0332]** The capsules, gelatin capsules, caplets, tablets, chewable tablets, powders or granules, used for the oral administration of at least one compound of Formula (I) and

**[0333]** Formula (II) are prepared by admixing at least one compound of Formula (I) and Formula (II) (active ingredient) together with at least one excipient using conventional pharmaceutical compounding techniques. Non-limiting examples of excipients used in oral dosage forms described herein include, but are not limited to, binders, fillers, disintegrants, lubricants, absorbents, colorants, flavors, preservatives and sweeteners.

**[0334]** Non-limiting examples of such binders include, but are not limited to, corn starch, potato starch, starch paste, pre-gelatinized starch, or other starches, sugars, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, tragacanth, guar gum, cellulose and its derivatives (by way of example only, ethyl cellulose, cel-

lulose acetate, carboxymethyl cellulose calcium, sodium carboxymethylcellulose, methyl cellulose, hydroxypropyl methylcellulose and microcrystalline cellulose), magnesium aluminum silicate, polyvinyl pyrrolidone and combinations thereof.

**[0335]** Non-limiting examples of such fillers include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. In certain embodiments, the binder or filler in pharmaceutical compositions provided herein are present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

**[0336]** Non-limiting examples of such disintegrants include, but are not limited to, agar-agar, alginic acid, sodium alginate, calcium carbonate, sodium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, other starches, clays, other alginates, other celluloses, gums, and combinations thereof. In certain embodiments, the amount of disintegrant used in the pharmaceutical compositions provided herein is from about 0.5 to about 15 weight percent of disintegrant, while in other embodiments the amount is from about 1 to about 5 weight percent of disintegrant.

**[0337]** Non-limiting examples of such lubricants include, but are not limited to, sodium stearate, calcium stearate, magnesium stearate, stearic acid, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, sodium lauryl sulfate, talc, hydrogenated vegetable oil (by way of example only, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, sodium oleate, ethyl oleate, ethyl laureate, agar, silica, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, Md.), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, Tex.), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass.) and combinations thereof. In certain embodiments, the amount of lubricants used in the pharmaceutical compositions provided herein is in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms.

**[0338]** Non-limiting examples of such diluents include, but are not limited to, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycine or combinations thereof.

**[0339]** In certain embodiments, tablets and capsules are prepared by uniformly admixing at least one compound of Formula (I) or Formula (II) (active ingredients) with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary. In certain embodiments, tablets are prepared by compression. In other embodiments, tablets are prepared by molding.

**[0340]** In certain embodiments, at least one compound of Formula (I) or Formula (II) is orally administered as a controlled release dosage form. Such dosage forms are used to provide slow or controlled-release of one or more compounds of Formula (I) or Formula (II). Controlled release is obtained using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof. In certain embodiments, controlled-release dosage forms are used to extend activity of

the compound of Formula (I) or Formula (II), reduce dosage frequency, and increase patient compliance.

**[0341]** Administration of compounds of Formula (I) or Formula (II) as oral fluids such as solution, syrups and elixirs are prepared in unit dosage forms such that a given quantity of solution, syrups or elixirs contains a predetermined amount of a compound of Formula (I) or Formula (II). Syrups are prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions are formulated by dispersing the compound in a non-toxic vehicle. Non-limiting examples of excipients used in as oral fluids for oral administration include, but are not limited to, solubilizers, emulsifiers, flavoring agents, preservatives, and coloring agents. Non-limiting examples of solubilizers and emulsifiers include, but are not limited to, water, glycols, oils, alcohols, ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers. Non-limiting examples of preservatives include, but are not limited to, sodium benzoate. Non-limiting examples of flavoring agents include, but are not limited to, peppermint oil or natural sweeteners or saccharin or other artificial sweeteners.

#### Parenteral Dosage Forms

**[0342]** In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II) are administered parenterally by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial.

**[0343]** Such parenteral dosage forms are administered in the form of sterile or sterilizable injectable solutions, suspensions, dry and/or lyophilized products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection (reconstitutable powders) and emulsions. Vehicles used in such dosage forms include, but are not limited to, Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

#### Transdermal Dosage Forms

**[0344]** In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II) are administered transdermally. Such transdermal dosage forms include "reservoir type" or "matrix type" patches, which are applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of a compound of Formula (I) or Formula (II). By way of example only, such transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. In other embodiments, matrix transdermal formulations are used.

**[0345]** Formulations for transdermal delivery of a compound of Formula (I) or Formula (II) include an effective amount of a compound of Formula (I) or Formula (II), a

carrier and an optional diluent. A carrier includes, but is not limited to, absorbable pharmacologically acceptable solvents to assist passage through the skin of the host, such as water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and combinations thereof.

**[0346]** In certain embodiments, such transdermal delivery systems include penetration enhancers to assist in delivering one or more compounds of Formula (I) or Formula (II) to the tissue. Such penetration enhancers include, but are not limited to, acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

**[0347]** In other embodiments, the pH of such a transdermal pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, is adjusted to improve delivery of one or more compounds of Formula (I) or Formula (II). In other embodiments, the polarity of a solvent carrier, its ionic strength, or tonicity are adjusted to improve delivery. In other embodiments, compounds such as stearates are added to advantageously alter the hydrophilicity or lipophilicity of one or more compounds of Formula (I) or Formula (II) so as to improve delivery. In certain embodiments, such stearates serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. In other embodiments, different salts, hydrates or solvates of the compounds of Formula (I) or Formula (II) are used to further adjust the properties of the resulting composition.

**[0348]** In certain embodiments compounds of Formula (I) or Formula (II) are transdermally delivered from a patch by iontophoresis.

#### Topical Dosage Forms

**[0349]** In certain embodiments at least one compound of Formula (I) or Formula (II) is administered by topical application of pharmaceutical composition containing at least one compound of Formula (I) or Formula (II) in the form of lotions, gels, ointments solutions, emulsions, suspensions or creams. Suitable formulations for topical application to the skin are aqueous solutions, ointments, creams or gels, while formulations for ophthalmic administration are aqueous solutions. Such formulations optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

**[0350]** Such topical formulations include at least one carrier, and optionally at least one diluent. Such carriers and diluents include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and combinations thereof.

**[0351]** In certain embodiments, such topical formulations include penetration enhancers to assist in delivering one or more compounds of Formula (I) or Formula (II) to the tissue. Such penetration enhancers include, but are not limited to, acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-soluble or

insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

#### Inhalation Administration

**[0352]** In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II) are administered by inhalation. Inhalation refers to administration into the patient's lungs whether inhaled through the mouth or through the nasal passages. Dosage forms for inhaled administration are formulated as aerosols, dry powders, suspensions, or solution compositions. Dry powder compositions contain at least one compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof as a finely divided powder together with one or more pharmaceutically-acceptable excipients as finely divided powders. Such pharmaceutically-acceptable excipients used in dry powders include, but are not limited to, lactose, starch, mannitol, and mono-, di-, and polysaccharides. In certain embodiments, the finely divided powder is prepared by micronisation and milling, wherein the size-reduced (micronised) compound is defined by a  $D_{50}$  value of about 1 to about 10 microns.

**[0353]** Aerosol formulations for inhalation administration comprise a solution or fine suspension of at least one compound of Formula (I) or Formula (II) in a pharmaceutically acceptable aqueous or non-aqueous solvent/propellant. Suitable propellants include halocarbons, hydrocarbons, and other liquified gases. Representative propellants include: trichlorofluoromethane (propellant 11), dichlorofluoromethane (propellant 12), dichlorotetrafluoroethane (propellant 14), tetrafluoroethane (HFA-134a), 1,1-difluoroethane (HFA-152a), difluoromethane (HFA-32), pentafluoroethane (HFA-12), heptafluoropropane (HFA-227a), perfluoropropane, perfluorobutane, perfluoropentane, butane, isobutane, and pentane. In addition, such pharmaceutical compositions optionally comprise a powder base such as lactose, glucose, trehalose, mannitol or starch, and optionally a performance modifier such as L-leucine or another amino acid, and/or metals salts of stearic acid such as magnesium or calcium stearate. Aerosol also optionally contain additional pharmaceutically-acceptable excipients such as surfactants, lubricants, cosolvents and other excipients to improve the physical stability of the formulation, to improve solubility, or to improve taste.

**[0354]** The particle size of a micronized compound of Formula (I) or Formula (II) contained in an aerosol formulation is less than 100 microns, while in other embodiments less than 20 microns. In certain embodiments the particle size is in the range of from 1 to 10 microns, in other embodiments from 1 to 5 microns, while in still other embodiments from 2 to 3 microns.

**[0355]** Thus provided herein is a pharmaceutical aerosol formulation comprising at least one compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof and a fluorocarbon or hydrogen-containing chlorofluorocarbon as propellant, optionally in combination with a surfactant and/or a cosolvent. In certain embodiments, in such pharmaceutical aerosol formulation the propellant is selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane and mixtures thereof.

**[0356]** In certain embodiments, suspensions and solutions comprising at least one compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, formulated for inhalation administration are administered via a nebulizer.

The solvent or suspension agent utilized for nebulization is any pharmaceutically-acceptable liquid such as water, aqueous saline, alcohols or glycols, (by way of example only, ethanol, isopropylalcohol, glycerol, propylene glycol, polyethylene glycol or mixtures thereof). Saline solutions utilize salts which display little or no pharmacological activity after administration. Such salt include, but are not limited to, alkali metal or ammonium halogen salts or organic acids (by way of example only, ascorbic acid, citric acid, acetic acid and tartaric acid). Such suspensions optionally contain other pharmaceutically-acceptable excipients provided herein.

**[0357]** In certain embodiments, compounds of Formula (I) or Formula (II) are administered directly to the lung by inhalation using a Metered Dose Inhaler ("MDI"), which utilizes canisters that contain a suitable low boiling propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or a Dry Powder Inhaler (DPI) device which uses a burst of gas to create a cloud of dry powder inside a container, which is then be inhaled by the patient. In certain embodiments, capsules and cartridges of gelatin for use in an inhaler or insufflator are formulated containing a powder mixture of a compound of Formula (I) or Formula (II) and a powder base such as lactose or starch. In certain embodiments, compounds of Formula (I) or Formula (II) are delivered to the lung using a liquid spray device, wherein such devices use extremely small nozzle holes to aerosolize liquid drug formulations that can then be directly inhaled into the lung. In other embodiments, compounds of Formula (I) or Formula (II) are delivered to the lung using a nebulizer device, wherein a nebulizer creates an aerosols of liquid drug formulations by using ultrasonic energy to form fine particles that can be readily inhaled. In other embodiments, compounds of Formula (I) or Formula (II) are delivered to the lung using an electrohydrodynamic ("EHD") aerosol device wherein such EHD aerosol devices use electrical energy to aerosolize liquid drug solutions or suspensions.

**[0358]** In certain embodiments, the proportion of Formula (I) or Formula (II) or pharmaceutically acceptable salt thereof used in powders for inhalation or insufflation is within the range of from 0.1 to 10%. In other embodiments, the proportion of Formula (I) or Formula (II) or pharmaceutically acceptable salt thereof used in powders for inhalation or insufflation is within the range of from 0.1 to 5%. In certain embodiments, aerosol formulations contain from 20  $\mu\text{g}$  to 10 mg of a compound of Formula (I) or Formula (II), while in other embodiments, aerosol formulations contain from 20  $\mu\text{g}$  to 2000  $\mu\text{g}$  of a compound of Formula (I) or Formula (II). In certain embodiments, aerosol formulations contain from 20  $\mu\text{g}$  to 500  $\mu\text{g}$  of a compound of Formula (I) or Formula (II). In certain embodiments, a compound of Formula (I) or Formula (II) is administered once daily by inhalation administration, while in other embodiments a compound of Formula (I) or Formula (II) is administered several times daily by inhalation administration. By way of example only, such multiple daily dosages occur 2, 3, 4 or 8 times daily, giving for example 1, 2 or 3 doses each time.

**[0359]** In certain embodiments, the pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), or pharmaceutically acceptable salts and solvates thereof, described herein, also contain one or more absorption enhancers. In certain embodiments, such absorp-

tion enhancers include, but are not limited to, sodium glycolate, sodium caprate, N-lauryl- $\beta$ -D-maltopyranoside, EDTA, and mixed micelles.

**[0360]** In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II) are administered intranasally. The dosage forms for nasal administration are formulated as aerosols, solutions, drops, gels or dry powders. Aqueous formulations for administration to the lung or nose optionally include conventional excipients as provided herein, such as buffering agents, tonicity modifying agents and the like.

#### Rectal Administration

**[0361]** In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II) are administered rectally in the form of suppositories, enemas, ointment, creams rectal foams or rectal gels. In certain embodiments such suppositories are prepared from fatty emulsions or suspensions, cocoa butter or other glycerides.

**[0362]** In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II) are administered ophthalmically as eye drops. Such formulations are aqueous solutions that optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

#### Otic Administration

**[0363]** In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II) are administered otically as ear drops. Such formulations are aqueous solutions that optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

#### Depot Administration

**[0364]** In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II) are formulated as a depot preparation. Such formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. In certain embodiments, such formulations include polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

#### Combination Treatment

**[0365]** In certain embodiments, a compound of Formula (I) or Formula (II) of the present invention, or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II) provided herein, is administered alone (without an additional therapeutic agent) for the treatment of a disease or disorder associated with c-kit kinase activity.

**[0366]** In certain embodiments, a compound of Formula (I) or Formula (II) of the present invention, or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a phar-

maceutical composition containing at least one compound of Formula (I) or Formula (II) provided herein, is administered alone (without an additional therapeutic agent) for the treatment of a disease or disorder associated with c-kit kinase activity and PDGFR ( $\alpha$  and/or  $\beta$ ) kinase activity.

**[0367]** In other embodiments, a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), is administered in combination with one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity.

**[0368]** In other embodiments, a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), is administered in combination with one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity and PDGFR ( $\alpha$  and/or  $\beta$ ) kinase activity.

**[0369]** In other embodiments, a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), is formulated in combination with one or more additional therapeutic agents and administered for the treatment of a disease or disorder associated with c-kit kinase activity.

**[0370]** In other embodiments, a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), is formulated in combination with one or more additional therapeutic agents and administered for the treatment of a disease or disorder associated with c-kit kinase activity and PDGFR ( $\alpha$  and/or  $\beta$ ) kinase activity.

**[0371]** In other embodiments, a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), is administered sequentially with one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity.

**[0372]** In other embodiments, a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), is administered sequentially with one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity and PDGFR ( $\alpha$  and/or  $\beta$ ) kinase activity.

**[0373]** In other embodiments, the combination treatments provided herein include administration of a compound of

Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), prior to administration of one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity.

**[0374]** In other embodiments, the combination treatments provided herein include administration of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), prior to administration of one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity and PDGFR ( $\alpha$  and/or  $\beta$ ) kinase activity.

**[0375]** In other embodiments, the combination treatments provided herein include administration of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), subsequent to administration of one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity.

**[0376]** In other embodiments, the combination treatments provided herein include administration of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), subsequent to administration of one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity and PDGFR ( $\alpha$  and/or  $\beta$ ) kinase activity.

**[0377]** In certain embodiments, the combination treatments provided herein include administration of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), concurrently with one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity.

**[0378]** In certain embodiments, the combination treatments provided herein include administration of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), concurrently with one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity and PDGFR ( $\alpha$  and/or  $\beta$ ) kinase activity.

**[0379]** In certain embodiments of the combination therapies described herein, the compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and the additional therapeutics agent(s) act additively. In certain embodiments of the combination therapies described herein, the compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and the additional therapeutics agent(s) act synergistically.

ically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and the additional therapeutics agent(s) act additively. In certain embodiments of the combination therapies described herein, the compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and the additional therapeutics agent(s) act synergistically.

**[0380]** The additional therapeutic agents used in combination with at least one compound of Formula (I) or Formula (II) of the present invention, or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to antiemetic agents, anti-inflammatory agents, immunomodulatory agents, cytokines, antidepressants, hormones, alkylating agents, antimetabolites, antitumour antibiotics, antimitotic agents, topoisomerase inhibitors, cytostatic agents, anti-invasion agents, antiangiogenic agents, inhibitors of growth factor function, anticancer agents and toll-like receptor modulators.

**[0381]** In some embodiments, the compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are used in combination with a second therapeutic agent for treating asthma. In certain combinations, the second therapeutic agent is a bronchodilator, an anti-inflammatory agent, a leukotriene antagonist, or an IgE blocker.

**[0382]** The antiemetic agents used in combination with compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, metoclopramide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine, acetylleucine monoethanolamine, alizapride, azasetron, benzquinamide, biefanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine, methallatal, metopimazine, nabilone, oxypemdyll, pipamazine, scopolamine, sulphiride, tetrahydrocannabinols, thiethylperazine, thioproperazine, tropisetron, and combinations thereof.

**[0383]** The anti-inflammatory agents used in combination with compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, non-steroidal anti-inflammatory drugs such as salicylic acid, acetylsalicylic acid, methyl salicylate, diflunisal, salsalate, olsalazine, sulfasalazine, acetaminophen, indomethacin, sulindac, etodolac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, dichlofenac, ibuprofen, naproxen, naproxen sodium, fenoprofen, ketoprofen, flurbiprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, droxicam, pivoxicam, tenoxicam, nabumetome, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, apazone and nimesulide, leukotriene antagonists including, but not limited to, zileuton, aurothioglucose, gold sodium thiomalate and auranofin, ste-



roids including, but not limited to, alclometasone dipropionate, amcinonide, beclomethasone dipropionate, betametasone, betamethasone benzoate, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone valerate, clobetasol propionate, clocortolone pivalate, hydrocortisone, hydrocortisone derivatives, desonide, desoximetasone, dexamethasone, flunisolide, flucocinolide, flurandrenolide, halcinonide, medrysone, methylprednisolone, methprednisolone acetate, methylprednisolone sodium succinate, mometasone furoate, paramethasone acetate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebutate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate, and triamcinolone hexacetonide and other anti-inflammatory agents including, but not limited to, methotrexate, colchicine, allopurinol, probenecid, thalidomide or a derivative thereof, 5-aminosalicylic acid, retinoid, dithranol or calcipotriol, sulfapyrazone and benzbromarone.

**[0384]** The immunomodulatory agents used in combination with compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, azathioprine, tacrolimus, cyclosporin methotrexate, leflunomide, corticosteroids, cyclophosphamide, cyclosporine A, cyclosporin G, mycophenolate mofetil, ascromycin, rapamycin (sirolimus), FK-506, mizoribine, deoxyispergualin, brequinar, mycophenolic acid, malononitriloamides (such as, by way of example only, leflunamide), T cell receptor modulators, and cytokine receptor modulators, peptide mimetics, and antibodies (such as, by way of example only, human, humanized, chimeric, monoclonal, polyclonal, Fvs, ScFvs, Fab or F(ab)<sub>2</sub> fragments or epitope binding fragments), nucleic acid molecules (such as, by way of example only, antisense nucleic acid molecules and triple helices), small molecules, organic compounds, and inorganic compounds. Examples of T cell receptor modulators include, but are not limited to, anti-T cell receptor antibodies (such as, by way of example only, anti-CD4 antibodies (such as, by way of example only, cM-T412 (Boehringer), IDEC-CE9.1<sup>TM</sup> (IDEC and SKB), mAB 4162W94, Orthoclone and OKTcdr4a (Janssen-Cilag)), anti-CD3 antibodies (such as, by way of example only, Nuvion (Product Design Labs), OKT3 (Johnson & Johnson), or Rituxan (IDEC)), anti-CD5 antibodies (such as, by way of example only, an anti-CD5 ricin-linked immunoconjugate), anti-CD7 antibodies (such as, by way of example only, CHH-380 (Novartis)), anti-CD8 antibodies, anti-CD40 ligand monoclonal antibodies (such as, by way of example only, IDEC-131 (IDEC)), anti-CD52 antibodies (such as, by way of example only, CAMPATH 1H (Illex)), anti-CD2 antibodies, anti-CDIIa antibodies (such as, by way of example only, Xanelim (Genentech)), anti-B7 antibodies (such as, by way of example only, IDEC-114 (IDEC)), CTLA4-immunoglobulin, and toll receptor-like (TLR) modulators. Examples of cytokine receptor modulators include, but are not limited to, soluble cytokine receptors (such as, by way of example only, the extracellular domain of a TNF- $\alpha$  receptor or a fragment thereof, the extracellular domain of an IL-1 $\beta$  receptor or a fragment thereof, and the extracellular domain of an IL-6 receptor or a fragment thereof), cytokines or fragments thereof (such as, by way of example only, interleukin (IL)-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-15, TNF- $\alpha$ , interferon (IFN)- $\alpha$ , IFN- $\beta$ , IFN- $\gamma$ , and GM-CSF), anti-cytok-

ine receptor antibodies (such as, by way of example only, anti-IFN receptor antibodies, anti-IL-2 receptor antibodies (such as, by way of example only, Zenapax (Protein Design Labs)), anti-IL-4 receptor antibodies, anti-IL-6 receptor antibodies, anti-IL-10 receptor antibodies, and anti-IL-12 receptor antibodies), anti-cytokine antibodies (such as, by way of example only, anti-IFN antibodies, anti-TNF- $\alpha$  antibodies, anti-IL-1 $\beta$  antibodies, anti-IL-6 antibodies, anti-IL-8 antibodies (such as, by way of example only, ABX-IL-8 (Abgenix)), and anti-IL-12 antibodies).

**[0385]** The alkylating agents used in combination with compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, nitrogen mustards, ethylenimines, methylmelamines, alkyl sulfonates, nitrosoureas, carmustine, lomustine, triazines, melphalan, mechlorethamine, cisplatin, oxaliplatin, carboplatin, cyclophosphamide, ifosfamide, melphalan, chlorambucil, hexamethylmelaine, thiotepea, busulfan, carmustine, streptozocin, dacarbazine and temozolomide.

**[0386]** The antimetabolites used in combination with compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, cytarabine, gemcitabine and antifolates such as, by way of example only, fluoropyrimidines (by way of example only, 5-fluorouracil and tegafur), raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea.

**[0387]** The antitumor antibiotics used in combination with compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, anthracyclines, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin.

**[0388]** The antimetabolic agents used in combination with compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, vinca alkaloids (by way of example only, vincristine, vinblastine, vindesine and vinorelbine), taxoids (by way of example only, taxol, paclitaxel and taxotere) and polokinasase inhibitors.

**[0389]** The topoisomerase inhibitors used in combination with compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, epipodophyllotoxins by way of example only, etoposide and teniposide, amsacrine, topotecan, irinotecan and camptothecin.

**[0390]** In other embodiments, the combinations described herein include combination of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-

761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrazones; a methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2-cyanoquinoline compound such as L-746, 530; or an indole or quinoline compound such as MK-591, MK-886, and BAYx1005.

**[0391]** In other embodiments, the combinations described herein include combination of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a receptor antagonist for leukotrienes (LTB<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>) selected from the group consisting of the phenothiazin-3-Is such as L-651, 392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIII. 284260; and compounds such as zafirlukast, ablukast, montelukast, SINGULAIR™, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAYx7195.

**[0392]** In other embodiments, the combinations described herein include combination of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a phosphodiesterase (PDE) inhibitor such as a methylxanthanine including theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE4 inhibitor, including, but not limited to, cilomilast or roflumilast, an inhibitor of the isoform PDE4D, or an inhibitor of PDE5.

**[0393]** In other embodiments, the combinations described herein include combination of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine.

**[0394]** In other embodiments, the combinations described herein include combination of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a gastroprotective histamine type 2 receptor antagonist. In other embodiments, the combinations described herein include combination of a compound of Formula (I) and Formula (II), or a pharmaceutically acceptable salt or solvate thereof, described herein, with an antagonist of the histamine type 4 receptor.

**[0395]** In other embodiments, the combinations described herein include combination of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with an alpha-1alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride,

ride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.

**[0396]** In other embodiments, the combinations described herein include combination of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide or mometasone furoate.

**[0397]** In other embodiments, the combinations described herein include combination of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with an immunoglobulin (Ig), gamma globulin, Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (omalizumab).

**[0398]** In other embodiments, the combinations described herein include combination of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a chemotherapeutic agent to treat a cell proliferative disorder, including but not limited to, lymphoma, osteosarcoma, melanoma, or a tumor of breast, renal, prostate, colorectal, thyroid, ovarian, pancreatic, neuronal, lung, uterine or gastrointestinal tumor. Non-limiting examples of chemotherapeutic agents used in such combinations are anthracyclines, alkylating agents (e.g., mitomycin C), alkyl sulfonates, aziridines, ethylenimines, methylmelamines, nitrogen mustards, nitrosoureas, antibiotics, antimetabolites, folic acid analogs (e.g., dihydrofolate reductase inhibitors such as methotrexate), purine analogs, pyrimidine analogs, enzymes, podophyllotoxins, platinum-containing agents, interferons, and interleukins. Other non-limiting examples of chemotherapeutic agents used in such combinations are busulfan, improsulfan, piposulfan, benzodepa, carboquone, meturedopa, uredepa, altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenephosphoramide, triethylenethiophosphoramidate, trimethylololomelamine, chlorambucil, chlornaphazine, cyclophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine, dacarbazine, mannometrine, mitobronitol, mitolactol, pipobroman, aclacinomycins, actinomycin F(1), anthramycin, azaserine, bleomycin, cactinomycin, carubicin, carzino-philin, chromomycin, dactinomycin, daunorubicin, daunomycin, 6-diazo-5-oxo-1-norleucine, doxorubicin, epirubicin, mitomycin C, mycophenolic acid, nogalamycin, olivomycin, peplomycin, plicamycin, porfiromycin, puromycin, streptogrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, denopterin, methotrexate, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, fluorouracil, tegafur, L-asparaginase, pulmozyme, aceglatone, aldophosphamide glycoside, aminolevulinic acid, amsacrine, bestrabucil, bisantrene, carboplatin, cisplatin, defofamide, demecolcine, diaziquone, elformithine, elliptinium acetate, etoglucid, etoposide, flutamide, gallium nitrate, hydroxyurea,

interferon-alpha, interferon-beta, interferon-gamma, interleukin-2, lentinan, lonidamine, mitoguazone, mitoxantrone, mopidamol, nitracrine, pentostatin, phenamet, pirarubicin, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, sizofuran, spirogermanium, paclitaxel, tamoxifen, teniposide, tenuazonic acid, triaziquone, 2,2',2''-trichlorotriethylamine, urethane, vinblastine, vincristine, and vindesine.

**[0399]** In certain embodiments, the combination treatments provided herein include administration of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing a compound of Formula (I) and Formula (II) in combination with one or more additional therapeutic agents, for the treatment of Pulmonary Arterial Hypertension (PAH). Such additional therapeutic agents include phosphodiesterase-5 inhibitors, prostanoids, endothelin receptor antagonists, calcium channel blockers, oxygen therapy, iloprost, sildenafil, tadalafil, digoxin, furosemide, spironolactone, warfarin, epoprostenol, treprostinil, bosentan and ambrisentan.

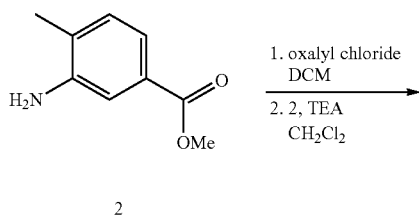
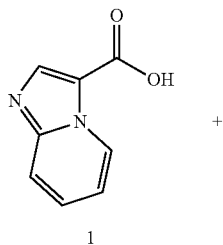
#### EXAMPLES

**[0400]** The following examples were offered to illustrate, but not to limit, the compounds of Formula (I) or Formula (II) of the present invention, and the preparation of such compounds.

#### Synthesis of Intermediates

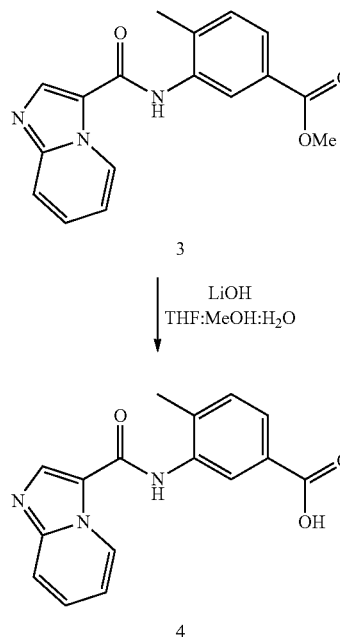
##### Synthesis of 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylbenzoic acid (4)

**[0401]**



1. oxalyl chloride  
DCM  
2. TEA  
CH<sub>2</sub>Cl<sub>2</sub>

-continued

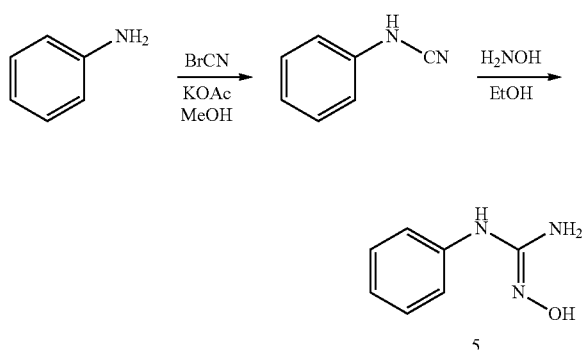


**[0402]** To a suspension of imidazo[1,2-a]pyridine-3-carboxylic acid (1) (4.09 g, 25.3 mmol) in dichloromethane (100 mL) and DMF (0.25 mL) at 0° C. was added oxalyl chloride (4.15 mL, 48.0 mmol) dropwise over 10 minutes. The reaction was slowly warmed to room temperature and stirred until complete conversion was detected by LCMS. The reaction was subsequently reduced to dryness and suspended in dichloromethane (100 mL) and was added a solution of methyl 3-amino-4-methylbenzoate (2) (4.6 g, 27.9 mmol) in dichloromethane (100 mL) and triethylamine (7.1 mL). Contents were stirred at room temperature for 4 hours and diluted with dichloromethane (100 mL). The reaction was washed with water, saturated NaHCO<sub>3</sub>, brine, dried over magnesium sulfate, filtered and reduced to dryness. The crude solid was triturated with diethyl ether to remove excess aniline and dried to afford methyl 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylbenzoate (3) as a white solid. MS m/z 310.1 (M+1)<sup>+</sup>.

**[0403]** To a suspension of 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylbenzoate (3) (5.43 g, 17.6 mmol) in THF (225 mL) and MeOH (150 mL) was added LiOH 3 M (17.5 mL) and water (50 mL). The reaction was stirred at room temperature for 12 hours then reduced in volume on roto-vap to remove THF and MeOH. The mixture was diluted with water (75 mL) and neutralized with HCl (17.5 mL of a 3M solution). The resulting precipitate was filtered, washed with water and dried under vacuum to afford 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylbenzoic acid (4) as a white solid. <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.0 (s, 1H), 9.45 (dt, J=6.8, 1.2 Hz, 1H), 8.58 (s, 1H), 7.98 (d, J=2.0 Hz, 1H), 7.79 (dt, J=9.2, 1.2 Hz, 1H), 7.76 (dd, J=8.0, 1.6 Hz, 1H), 7.52 (ddd, J=9.2, 9.2, 1.2 Hz, 1H), 7.43 (d, J=8.0 Hz, 1H), 7.17 (td, J=6.8, 1.2 Hz, 1H), 2.35 (s, 3H). MS m/z 296.1 (M+1)<sup>+</sup>.

## Synthesis of 2-hydroxy-1-phenylguanidine (5)

[0404]

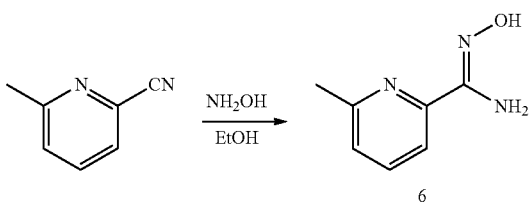


**[0405]** To a solution of BrCN (0.11 g, 1.1 mmol) in MeOH (10 mL) at 0° C. was added solid KOAc (0.32 g, 3.3 mmol) and a solution of aniline (0.1 mL, 1.1 mmol) in MeOH (1 mL). The reaction was stirred for 3 hours then partitioned with water (15 mL) and dichloromethane (25 mL). The organic layer was separated, washed with brine, dried over magnesium sulfate, filtered and reduced to dryness to afford N-phenylcyanamide, which was immediately used without purification.

**[0406]** N-phenylcyanamide was dissolved in EtOH (7 mL) and treated with H<sub>2</sub>NOH (1.5 eq of a 50% aq solution). The mixture was stirred at room temperature for 12 hours then reduced to dryness to afford 2-hydroxy-1-phenylguanidine (5) as a clear yellow oil, which was used without purification.

## Synthesis of N'-hydroxy-6-methylpicolinimidamide (6)

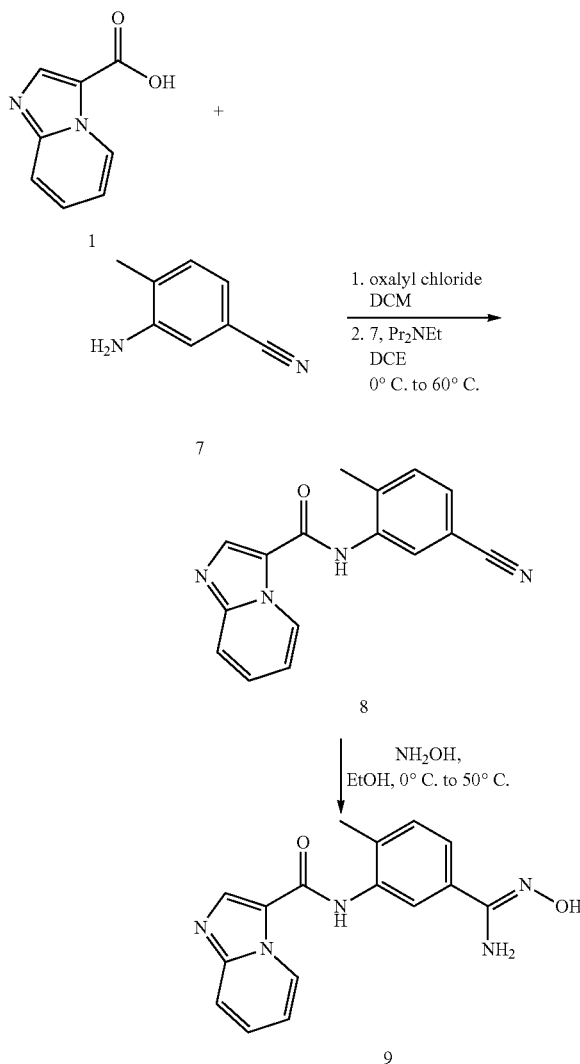
[0407]



**[0408]** 6-Methylpicolinonitrile (12 mg, 0.1 mmol) was dissolved in EtOH (0.5 mL) and treated with NH<sub>2</sub>OH (1.5 eq of a 50% aq solution). The mixture was stirred at room temperature for 12 hours then reduced to dryness to afford N'-hydroxy-6-methylpicolinimidamide (6) as a clear yellow oil, which was used without purification.

## Synthesis of N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9)

[0409]



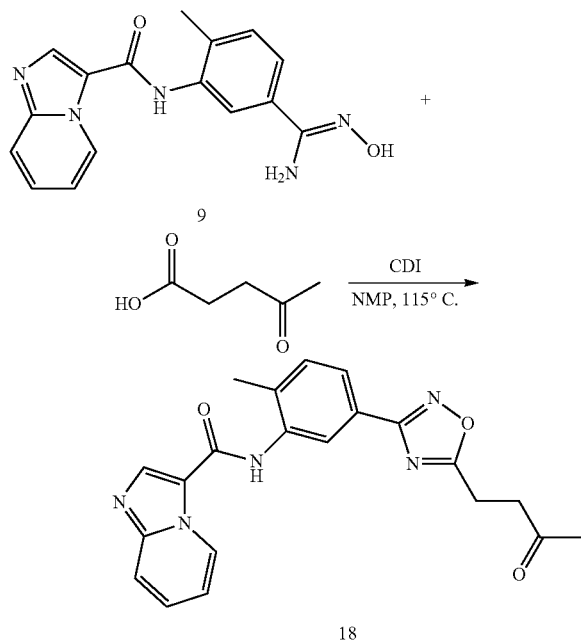
**[0410]** To a suspension of imidazo[1,2-a]pyridine-3-carboxylic acid (1) (16.6 g, 102 mmol) in dichloromethane (300 mL) and DMF (0.5 mL) at 0° C. was added oxalyl chloride (45 mL, 510 mmol) dropwise over 10 minutes. The reaction was slowly warmed to room temperature and stirred until complete conversion was detected by LCMS in MeOH. The reaction was subsequently reduced to dryness and suspended in dichloroethane (100 mL) and was added to a solution of 3-amino-4-methylbenzonitrile (7) (15 g, 113 mmol) in dichloroethane (200 mL) and Pr<sub>2</sub>NEt (55 mL) at 0° C. After the addition, the cold bath was removed and contents were stirred at room temperature for 1 hour and then heated to 50° C. for another 2 hours. After the completion of the reaction, the mixture was cooled and a white precipitate formed. The mixture was filtered and the solid was washed with cold dichloromethane. About 10 g of the desired N-(5-cyano-2-

methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (8) was obtained. The filtrate was washed with saturated  $\text{NH}_4\text{Cl}$ , saturated  $\text{NaHCO}_3$ , brine, dried over magnesium sulfate, filtered and reduced to dryness. The crude solid was triturated with diethyl ether to remove excess aniline and filtered to afford another crop of N-(5-cyano-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (8) as a white solid. MS  $m/z$  277.1 (M+1).

**[0411]** To a stirred and cooled ( $0^\circ\text{C}$ .) suspension of N-(5-cyano-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (8) (10 g, 36.2 mmol) in EtOH (225 ml) was added  $\text{NH}_2\text{OH}$  (6 mL, 50% in water solution). After the addition, the reaction was stirred at room temperature for 2 hours then heated at  $50^\circ\text{C}$ . for another 2 hours. After cooling to room temperature, the mixture was stored in the fridge overnight. The resulting precipitate was filtered, washed with cold EtOH and dried under vacuum to afford N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9) as a white solid.  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO)  $\delta$  9.40 (dt,  $J=6.8, 1.2$  Hz, 1H), 8.15 (s, 1H), 7.88 (d,  $J=2.0$  Hz, 1H), 7.79 (dt,  $J=9.2, 1.2$  Hz, 1H), 7.76 (dd,  $J=8.0, 1.6$  Hz, 1H), 7.52 (ddd,  $J=9.2, 9.2, 1.2$  Hz, 1H), 7.43 (d,  $J=8.0$  Hz, 1H), 7.17 (td,  $J=6.8, 1.2$  Hz, 1H), 2.49 (s, 3H). MS  $m/z$  310.1 (M+1) $^+$ .

Synthesis of N-(2-methyl-5-(5-(3-oxobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (18)

**[0412]**

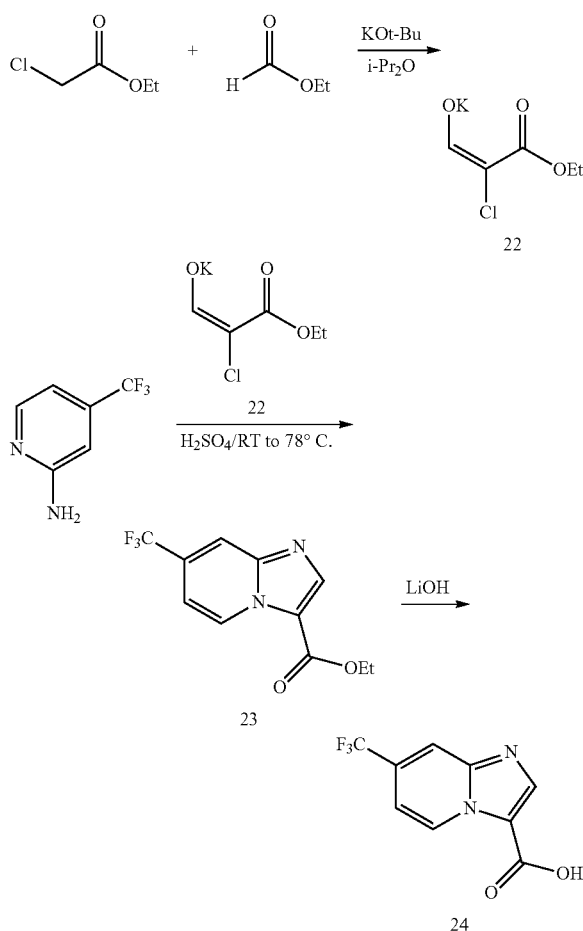


**[0413]** To a stirring solution of levulinic acid (188 mg, 1.62 mmol) in anhydrous NMP (2.5 mL) was added 1,1'-carbonyldiimidazole (CDI) (262 mg, 1.62 mmol). The reaction was stirred for 3 minutes. N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9) (250 mg, 0.808 mmol) was added and the reaction was stirred for 25 minutes. Then, the reaction was heated at  $115^\circ\text{C}$ . for 12

minutes. The crude reaction was purified by reverse phase preparative HPLC to give N-(2-methyl-5-(5-(3-oxobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (18).  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO)  $\delta$  10.17 (s, 1H), 9.52-9.50 (m, 1H), 8.69 (s, 1H), 8.04 (d,  $J=1.6$  Hz, 1H), 7.89-7.86 (m, 1H), 7.81 (dd,  $J=1.6, 7.6$  Hz, 1H), 7.69-7.65 (m, 1H), 7.51 (d,  $J=8.0$  Hz, 1H), 7.32-7.28 (m, 1H), 3.15-3.06 (m, 4H), 2.36 (s, 3H), 2.17 (s, 3H). MS  $m/z$  390.5 (M+1) $^+$ .

Synthesis of 7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (24)

**[0414]**



**[0415]** Ethyl 2-chloroacetate (20 mL, 187 mmol) and ethyl formate (15.1 mL, 187 mmol) were added simultaneously to a stirred and cooled suspension of potassium tert-butoxide (21.4 g, 188 mmol) in dry diisopropylether (300 mL). After the addition, the reaction was warmed to room temperature and stirred overnight. The yellow suspension was filtered and the solid potassium 2-chloro-3-ethoxy-3-oxoprop-1-en-1-olate (22) was vacuum dried and used directly in the following step.

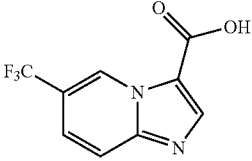
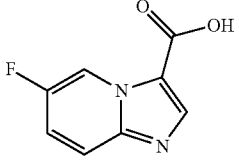
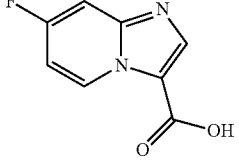
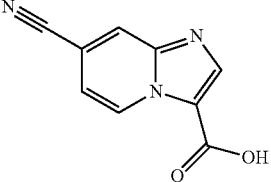
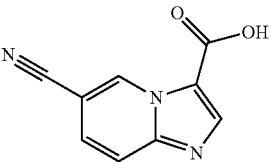
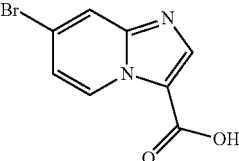
**[0416]** To a stirring suspension of 4-(trifluoromethyl)pyridin-2-amine (128 mg, 0.791 mmol) and potassium 2-chloro-3-ethoxy-3-oxoprop-1-en-1-olate (22) (500 mg, 2.64 mmol) in EtOH (5 mL) at room temperature was added sulfuric acid

(70  $\mu$ L, 1.32 mmol) dropwise. The reaction mixture was stirred at room temperature overnight then heated at 78° C. for 3 hours. The reaction was cooled to room temperature and the solvent was concentrated. The residue was taken in water and the pH was adjusted between 6-8 with saturated sodium bicarbonate. The crude product was extracted with ethyl acetate. The organic was washed with brine and dried over anhydrous sodium sulfate. The crude product 7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylate (23) was purified by silica chromatography. MS m/z 259.3 (M+1)<sup>+</sup>.

**[0417]** To a stirring solution of ethyl 7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylate (23) (100 mg, 0.387

mmol) in THF:MeOH (4:1, 1.5 mL) was added 2N LiOH (0.25 mL). The reaction was heated at 60° C. for 1 hour. Then, cooled to room temperature and the pH was adjusted between 4-5 with 1N HCl. The solvent was partially concentrated and the resulting aqueous layer was lyophilized to give 7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (24). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO)  $\delta$  9.44 (d, J=7.2 Hz, 1H), 8.40 (s, 1H), 8.31-8.30 (m, 1H), 7.48 (dd, J=2.0, 7.6 Hz, 1H). MS m/z 231.2 (M+1)<sup>+</sup>.

**[0418]** The following compounds were prepared according to the protocol described for 7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (24).

Intermediate number	Structure	Physical Data
24a		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 9.64-9.62 (m, 1H), 8.39 (s, 1H), 8.01 (d, J = 9.2 Hz, 1H), 7.81 (dd, J = 2.0, 9.2 Hz, 1H). MS m/z 231.2 (M + 1) <sup>+</sup> .
24b		MS m/z 181.2 (M + 1) <sup>+</sup> .
24c		MS m/z 181.2 (M + 1) <sup>+</sup> .
24d		MS m/z 188.1 (M + 1) <sup>+</sup> .
24e		MS m/z 188.1 (M + 1) <sup>+</sup> .
24f		MS m/z 241.0 (M + 1) <sup>+</sup> .

-continued

Intermediate number	Structure	Physical Data
24g		MS m/z 270.0 (M + 1) <sup>+</sup> .
24h		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) δ 8.94 (d, J = 2.0 Hz, 1H), 8.13 (s, 1H), 7.70 (d, J = 9.6 Hz, 1H), 7.31 (dd, J = 2.8, 9.8 Hz, 1H), 3.85 (s, 3H). MS m/z 193.1 (M + 1) <sup>+</sup> .
24i		MS m/z 177.6 (M + 1) <sup>+</sup> .
24j		MS m/z 177.6 (M + 1) <sup>+</sup> .
24k		MS m/z 209.06 (M + 1) <sup>+</sup> .
24l		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) δ 9.21 (s, 1H), 8.22 (s, 1H), 7.76 (d, J = 9.2 Hz, 1H), 7.50 (dd, J = 1.6, 9.2 Hz, 1H), 3.72-3.69 (m, 4H), 3.40-3.28 (m, 2H), 2.99-2.92 (m, 4H), 2.88-2.82 (m, 2H). MS m/z 276.13 (M + 1) <sup>+</sup> .
24m		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) δ 9.29 (d, J = 1.6 Hz, 1H), 9.15 (dd, J = 1.6, 4.4 Hz, 1H), 8.4 (s, 1H), 8.20 (d, J = 4.4 Hz, 1H). MS m/z 164.1 (M + 1) <sup>+</sup> .

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Intermediate number	Structure	Physical Data
24n		MS m/z 167.0 (M + 1) <sup>+</sup> .
24o		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) δ 8.79 (s, 1H), 8.49 (s, 1H), 7.84 (m, 2H), 3.80 (m, 4H), 3.16 (m, 4H). MS m/z 248.1 (M + 1) <sup>+</sup> .
24p		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) δ 9.69 (dd, J = 0.8, 2.0 Hz, 1H), 9.54 (s, 1H), 8.42 (s, 1H), 8.23 (s, 1H), 8.09 (dd, J = 0.8, 9.6 Hz, 1H), 7.95 (dd, J = 2.0, 9.6 Hz, 1H), 7.87 (s, 1H). MS m/z 248.1 (M + 1) <sup>+</sup> .
24q		MS m/z 216.0 (M + 1) <sup>+</sup> .
24r		MS m/z 205.0 (M + 1) <sup>+</sup> .
24s		MS m/z 270.0 (M + 1) <sup>+</sup> .
24t		MS m/z 207.1 (M + 1) <sup>+</sup> .
24u		MS m/z 243.1 (M + 1) <sup>+</sup> .

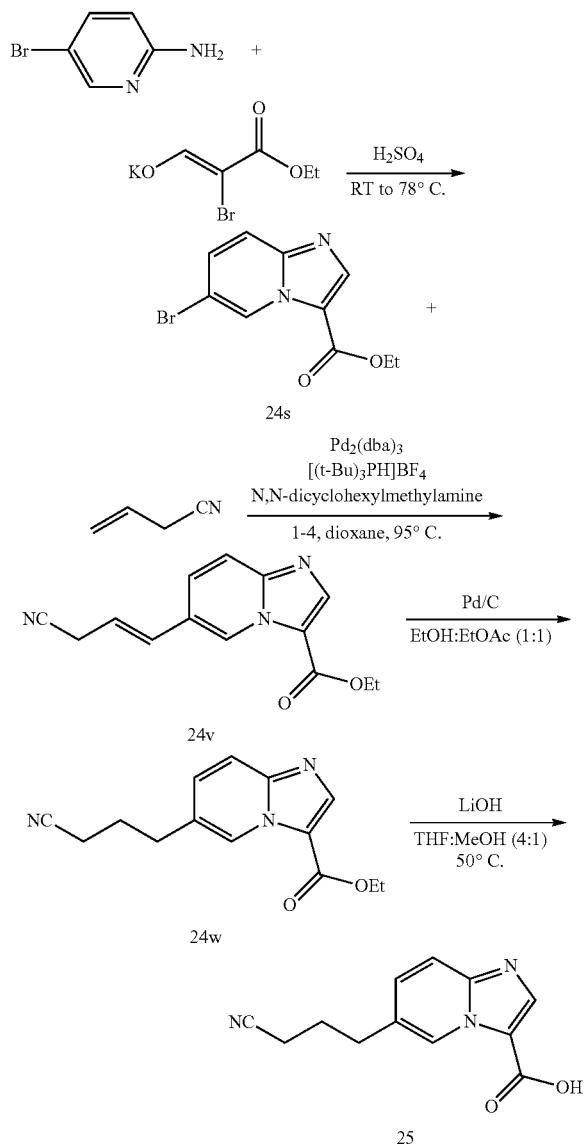


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Intermediate number	Structure	Physical Data
24v		MS m/z 241.0 (M + 1) <sup>+</sup> .

Synthesis of 6-(3-cyanopropyl)imidazo[1,2-a]pyridine-3-carboxylic acid (25)

[0419]



**[0420]** To a stirring suspension of 5-bromopyridin-2-amine (1.2 g, 7.05 mmol) and ethyl 2-chloro-3-hydroxyacrylate potassium salt (6.6 g, 28.19 mmol) (prepared in a similar manner as 22) in EtOH (100 mL) at room temperature was added sulfuric acid (751  $\mu$ L, 14.10 mmol) dropwise. The reaction mixture was heated at 78°C overnight. The reaction was cooled to room temperature and the solvent was concentrated. The residue was taken in water and the pH was adjusted between 6-8 with saturated sodium bicarbonate. The crude product was extracted with ethyl acetate. The organic was washed with brine and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography to yield ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (24s). MS m/z 270.2 (M+1)<sup>+</sup>.

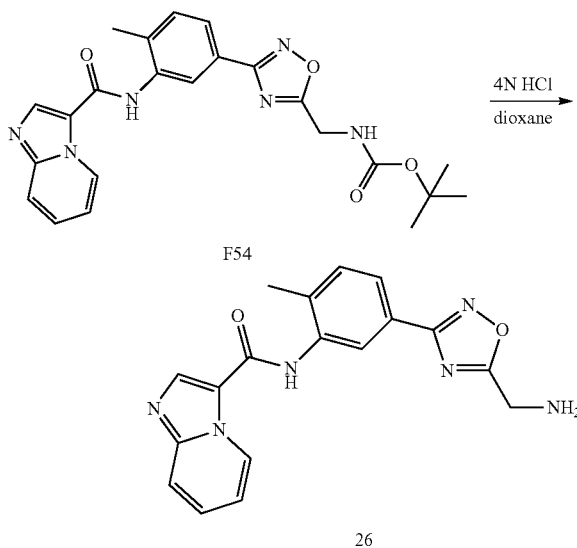
**[0421]** A stirring mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (24s) (500 mg, 1.86 mmol), allyl cyanide (224  $\mu$ L, 2.79 mmol), tris(dibenzylideneacetone)dipalladium(0) (26 mg, 0.028 mmol), [(t-Bu)<sub>3</sub>PH]BF<sub>4</sub> (16 mg, 0.056 mmol), and N,N-dicyclohexylmethylamine (433  $\mu$ L, 2.04 mmol) in anhydrous 1,4-dioxane (6 mL) was heated at 95°C overnight. The reaction was cooled to room temperature and filtered. The solvent was concentrated. The crude product was purified by silica chromatography to give ethyl 6-(3-cyanoprop-1-enyl)imidazo[1,2-a]pyridine-3-carboxylate (24v). MS m/z 256.4 (M+1)<sup>+</sup>.

**[0422]** To a stirring solution of ethyl 6-(3-cyanoprop-1-enyl)imidazo[1,2-a]pyridine-3-carboxylate (24v) (400 mg, 1.57 mmol) in EtOH:EtOAc (1:1, 10 mL) was added catalytic Pd/C (10 wt %, wet basis). The reaction was hydrogenated by balloon overnight then filtered through celite. The crude product ethyl 6-(3-cyanopropyl)imidazo[1,2-a]pyridine-3-carboxylate (24w) was used in the next step without further purification. MS m/z 258.4 (M+1)<sup>+</sup>.

**[0423]** To a stirring solution of ethyl 6-(3-cyanopropyl)imidazo[1,2-a]pyridine-3-carboxylate (24w) (375 mg, 1.46 mmol) in THF:MeOH (4:1, 5 mL) was added 2N LiOH (500  $\mu$ L). The reaction was heated at 50°C for 45 minutes then cooled to room temperature and the pH was adjusted between 3-4 with 1N HCl. The solvent was partially concentrated and the remaining aqueous was lyophilized to yield 6-(3-cyanopropyl)imidazo[1,2-a]pyridine-3-carboxylic acid (25). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO)  $\delta$  9.21-9.19 (m, 1H), 8.45 (s, 1H), 7.85 (dd, J=0.8, 9.2 Hz, 1H), 7.70 (dd, J=1.6, 9.2 Hz, 1H), 2.82 (t, J=7.2 Hz, 2H), 2.55 (t, J=7.2 Hz, 2H), 1.97-1.90 (m, 2H). MS m/z 230.3 (M+1)<sup>+</sup>.

Synthesis of N-(5-(5-(aminomethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (26)

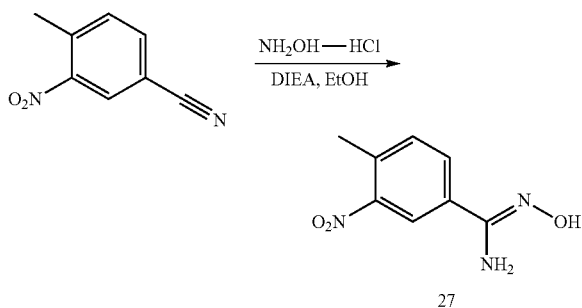
[0424]



[0425] To a stirring suspension of tert-butyl (3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methyl(methyl)carbamate (F54) (90 mg, 0.195 mmol) in acetonitrile (1 mL) was added 4N HCl in dioxane (1 mL) and water (0.5 mL). The reaction mixture was stirred at room temperature for 45 minutes. Then, the solvent was concentrated and the crude product was dried under high vacuum. The crude product N-(5-(5-(aminomethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (26) was used in the next step without further purification. <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.04 (s, 1H), 9.46-9.44 (m, 1H), 8.74 (s, 2H), 8.63 (s, 1H), 8.15 (d, J=2.0 Hz, 1H), 7.86-7.80 (m, 2H), 7.59-7.54 (m, 1H), 7.55 (d, J=8.4 Hz, 1H), 7.23-7.20 (m, 1H), 4.62 (s, 2H), 2.39 (s, 3H). MS m/z 349.4 (M+1)<sup>+</sup>.

Synthesis of (Z)-N<sup>1</sup>-hydroxy-4-methyl-3-nitrobenzimidamide (27)

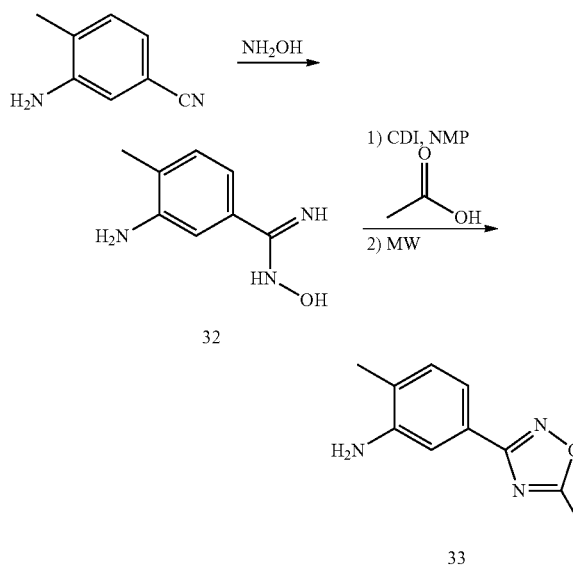
[0426]



[0427] A stirring mixture of 4-methyl-3-nitrobenzonitrile (2 g, 12.33 mmol), hydroxylamine hydrogen chloride (1 g, 14.80 mmol) and N,N-diisopropylethylamine (3.2 mL, 18.50 mmol) in EtOH (20 mL) was heated at 78° C. for 3 hours. Then, the solvent was concentrated and the crude product was dried under high vacuum. The crude product was taken in water and the solid was collected by vacuum filtration. The crude product (Z)—N<sup>1</sup>-hydroxy-4-methyl-3-nitrobenzimidamide (27) was used in the next step without further purification. MS m/z 196.3 (M+1)<sup>+</sup>.

Synthesis of 2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)aniline (33)

[0428]

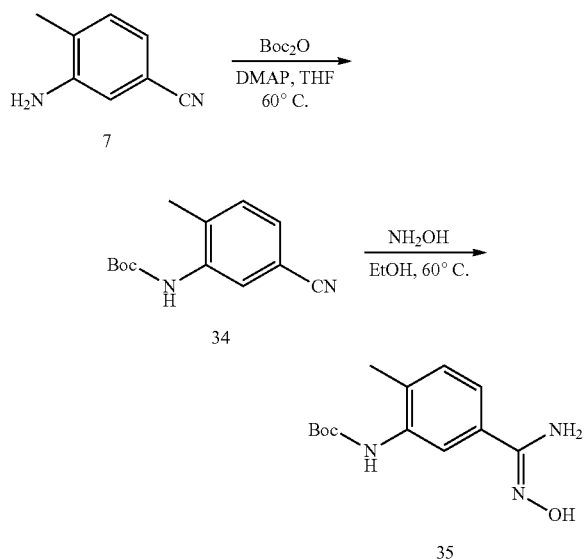


[0429] A mixture of 3-amino-4-methylbenzonitrile (1.32 g, 10 mmol) and NH<sub>2</sub>OH (50% wt. aqueous, 3.96 g, 60 mmol) in EtOH (15 mL) was refluxed at 70° C. overnight. After the reaction was completed, solvents were removed under vacuum to afford 3-amino-N-hydroxy-4-methylbenzimidamide (32) in quantitative yield. MS m/z 166.1 (M+1)<sup>+</sup>.

[0430] To a solution of acetic acid (0.72 g, 12 mmol) in NMP (15 mL) was slowly added CDI (1.94 g, 12 mmol). The resulting mixture was stirred at room temperature for 30 minutes. Then 3-amino-N-hydroxy-4-methylbenzimidamide (32) (1.66 g, 10 mmol) was added and stirred for another 30 minutes. LCMS showed the coupling reaction was completed and then the reaction mixture was heated at 125° C. for 15 minutes via microwave. The reaction mixture was poured into water (100 mL), extracted with EtOAc (2×50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude product was purified by silica-gel chromatography (0-50% EtOAc in hexanes) to afford 2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)aniline (33) (1.14 g, 60% yield). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 7.28 (d, J=1.6 Hz, 1H), 7.05-7.11 (m, 2H), 5.17 (s, 2H), 2.63 (s, 3H), 2.10 (s, 3H). MS m/z 190.1 (M+1)<sup>+</sup>.

Synthesis of tert-butyl 5-(N'-hydroxycarbamimidoyl)-2-methylphenylcarbamate (35)

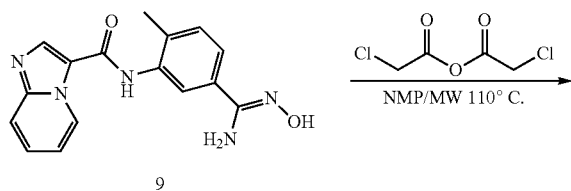
[0431]



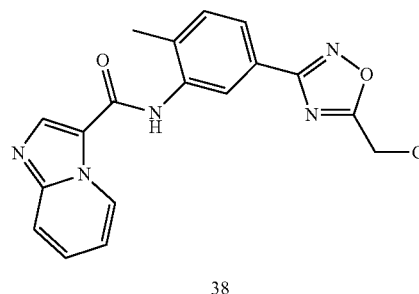
[0432] (Boc)<sub>2</sub>O (50 g, 227 mmol) was added portion-wise to a stirred solution of 3-amino-4-methylbenzonitrile (7) (10 g, 75.7 mmol) and DMAP (0.5 g) in THF (250 mL). After 30 minutes, the reaction was heated at 60° C. overnight. The crude reaction mixture was purified over silica gel to obtain a white solid tert-butyl 5-cyano-2-methylphenylcarbamate (34) (17.5 g, quantitative yield). MS m/z 233.1 (M+1)<sup>+</sup>. NH<sub>2</sub>OH (20 mL, 50% in water) was added to a stirred solution of tert-butyl 5-cyano-2-methylphenylcarbamate (34) (17.5 g, 75.3 mmol) in EtOH (200 mL) and the resulting solution was heated at 50° C. for 10 hours. The solvent was then evaporated and the product was titrated with EtOAc and hexane to obtain a white solid (Z)-tert-butyl 5-(N'-hydroxycarbamimidoyl)-2-methylphenylcarbamate (35) in a quantitative yield which was used without further purification. MS m/z 266.1 (M+1)<sup>+</sup>.

Synthesis of N-(5-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (38)

[0433]



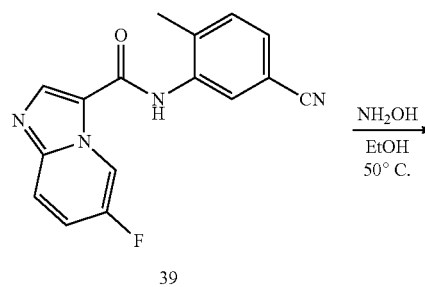
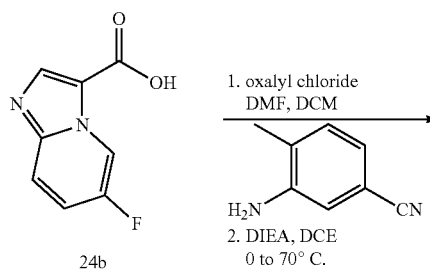
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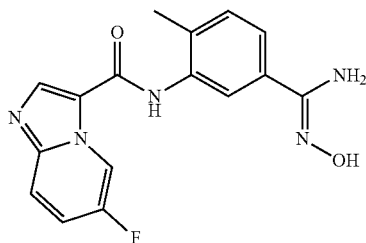
[0434] A mixture of N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9) (500 mg, 1.62 mmol) and 2-chloroacetic anhydride (553 mg, 3.23 mmol) in anhydrous NMP (10 mL) was heated in the microwave at 110° C. for 12 minutes. The crude was diluted with water and extracted with ethyl acetate. The organic was washed with a water/brine mixture and dried over anhydrous sodium sulfate. The solvent was concentrated and the crude product was purified by silica chromatography to yield N-(5-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (38). MS m/z 378.9 (M+1)<sup>+</sup>.

Synthesis of (Z)-6-fluoro-N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (40)

[0435]



-continued

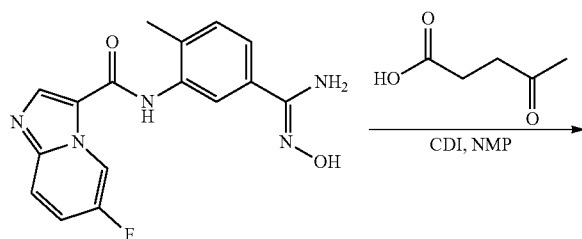


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**[0436]** Oxalyl chloride (10 mL, 110 mmol) was added dropwise to a stirred suspension of 6-fluoroimidazo[1,2-a]pyridine-3-carboxylic acid (24b) (2 g, 11 mmol) and catalytic amounts of DMF in dichloromethane (20 mL). After 5 hours, the solvent was evaporated and the solid was suspended in dry DCE (20 mL) and added to a stirred solution of 3-amino-4-methylbenzonitrile (1.45 g, 11 mmol) and DIEA (6 mmol) in DCE (10 mL) at 0° C. After the addition, the reaction was heated at 60° C. for 5 hours. The mixture was subjected to standard aqueous work and silica purification to give N-(5-cyano-2-methylphenyl)-6-fluoroimidazo[1,2-a]pyridine-3-carboxamide (39) as a solid. <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.14 (s, 1H), 9.45 (dd, J=5.2, 2.0 Hz, 1H), 8.62 (s, 1H), 7.90-7.87 (m, 2H), 7.68-7.63 (m, 1H), 7.53 (d, J=8.0 Hz, 1H), 2.37 (s, 3H). MS m/z 295.1 (M+1)<sup>+</sup>.

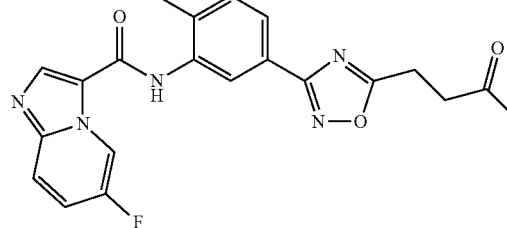
**[0437]** NH<sub>2</sub>OH (5 mL, 16.1 mmol) was added in one portion to a stirred suspension of N-(5-cyano-2-methylphenyl)-6-fluoroimidazo[1,2-a]pyridine-3-carboxamide (39) (0.95 g, 3.23 mmol). The resulting suspension was heated at 60° C. overnight and then cooled to 0° C. The product, (Z)-6-fluoro-N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (40) was collected by filtration. MS m/z 328.1 (M+1)<sup>+</sup>.

Synthesis of 6-fluoro-N-(2-methyl-5-(5-(3-oxobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (41)

**[0438]**

40

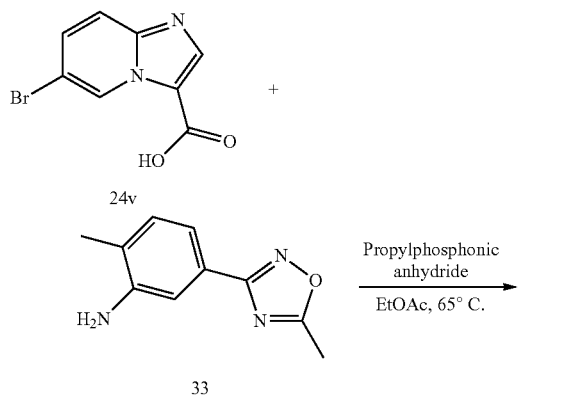
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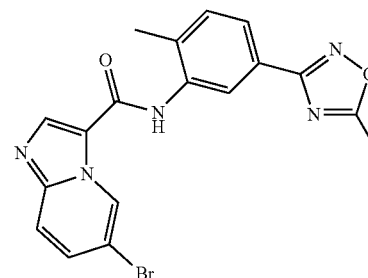
41

**[0439]** Carbonyl diimidazole (CDI) (34 mg, 0.2 mmol) was added to a stirred solution of 4-oxopentanoic acid (30 mg, 0.21 mmol). After 20 minutes, 6-fluoro-N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (40) (60 mg, 0.18 mmol) was added in one portion and the resulting solution was stirred for 1 hour before it was heated at 120° C. for 25 minutes in a microwave reactor. The reaction solution was subjected to standard aqueous work up and silica purification to give 6-fluoro-N-(2-methyl-5-(5-(3-oxobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (41). MS m/z 408.1 (M+1)<sup>+</sup>.

Synthesis of 6-bromo-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (42)

**[0440]**

33



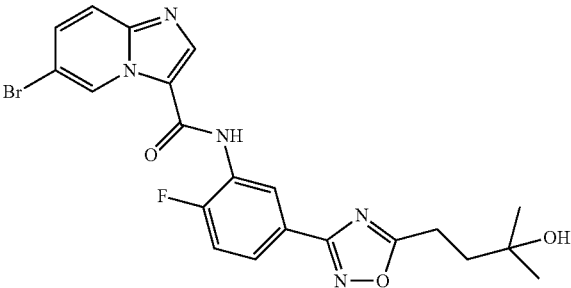
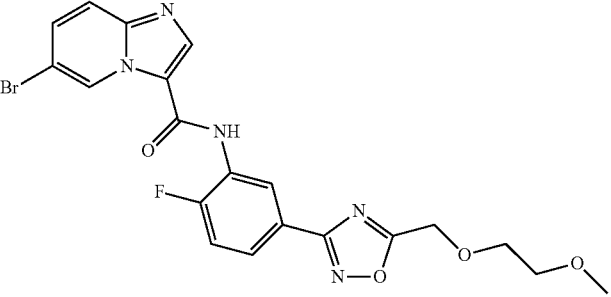
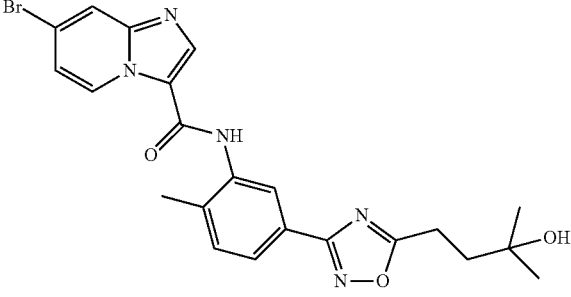
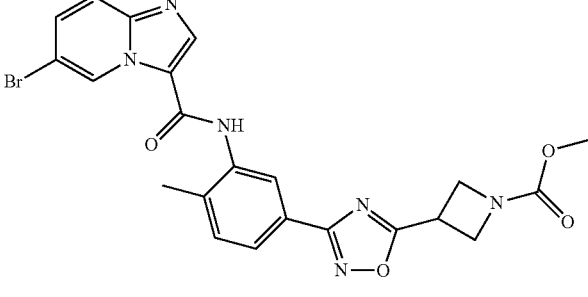
42

**[0441]** To a stirring suspension of 6-bromoimidazo[1,2-a]pyridine-3-carboxylic acid (24v) (637 mg, 2.64 mmol) and 2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)aniline (33) (500 mg, 2.64 mmol) in ethylacetate (8 mL) was added pro-

pylphosphonic anhydride solution 50 wt. % in ethyl acetate (3.1 mL, 5.29 mmol). The reaction was heated at 65° C. overnight. The reaction was cooled to room temperature and diluted with a solution of saturated sodium bicarbonate. The organic was separated and washed with 2× water/brine mixture and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography, DCM:EtOAc:MeOH (1:1:0.1) to yield 6-bromo-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyri-

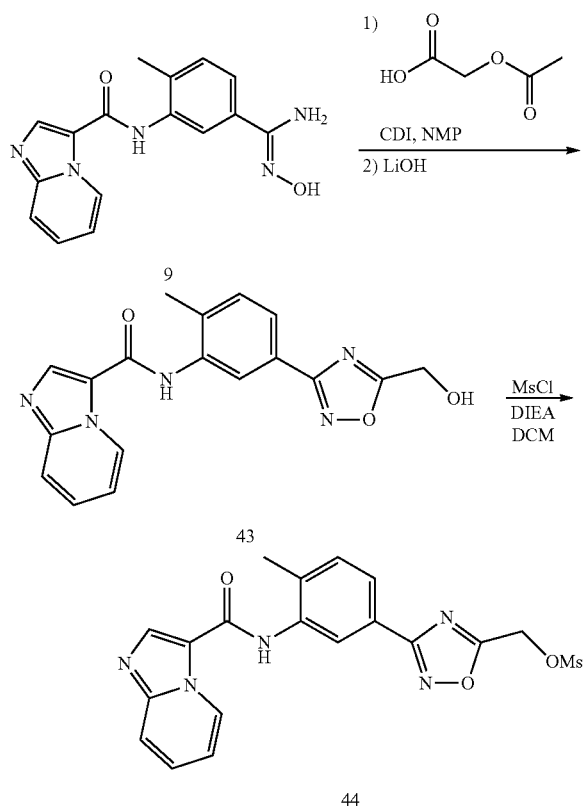
dine-3-carboxamide (81%, 42). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.13 (s, 1H), 9.63-9.62 (m, 1H), 8.60 (s, 1H), 8.07 (d, J=2.0 Hz, 1H), 7.83-7.79 (m, 2H), 7.68 (dd, J=2.0, 9.6 Hz, 1H), 7.50 (d, J=8.0 Hz, 1H), 2.67 (s, 3H), 2.37 (s, 3H). MS m/z 412, 414 (M+1)<sup>+</sup>.

**[0442]** The following compounds were prepared according to the protocol described for 6-bromo-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)phenylimidazo[1,2-a]pyridine-3-carboxamide (42)

Intermediate number	Structure	Physical Data
42d		MS m/z 489.0, 491.0 (M + 1) <sup>+</sup> .
42e		<sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) δ 9.80 (d, J = 1.2 Hz, 1H), 9.17 (dd, J = 2.0, 7.6 Hz, 1H), 8.25 (s, 1H), 7.91 (m, 2H), 7.66-7.73 (m, 3H), 4.92 (s, 2H), 3.64-3.68 (m, 4H), 3.43 (s, 3H). MS m/z 490.0, 492.0 (M + 1) <sup>+</sup> .
42i		MS m/z 484.0, 486.0 (M + 1) <sup>+</sup> .
42j		MS m/z 511.0, 513.0 (M + 1) <sup>+</sup> .

Synthesis of (3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methyl methanesulfonate (44)

[0443]



[0444] Carbonyl diimidazole (CDI) (324 mg, 2.0 mmol) was added to a stirred solution of 2-acetoxyacetic acid (236 mg, 2.0 mmol) in NMP. After 20 minutes, N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9) (310 mg, 1.0 mmol) was added in one portion and the resulting solution was stirred for 1 hour before it was heated at 125° C. for 15 minutes in a microwave reactor. The reaction solution was subjected to standard aqueous work up to afford a residue which was hydrolyzed by lithium hydroxide monohydrate (252 mg, 6.0 mmol) in THF/MeOH/H<sub>2</sub>O (3:2:1). After removal of all solvents 2M NaHCO<sub>3</sub> (10 mL) was added. The precipitate was filtered and dried in air to afford N-(5-(5-(hydroxymethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (43). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.02 (s, 1H), 9.46 (d, J=6.8 Hz, 1H), 8.59 (s, 1H), 8.11 (s, 1H), 7.82 (m, 2H), 7.53 (m, 2H), 7.18 (m, 1H), 6.08 (m, 1H), 4.80 (d, J=6.0 Hz, 2H), 2.37 (s, 3H). MS m/z 350.1 (M+1)<sup>+</sup>.

[0445] To a solution of N-(5-(5-(hydroxymethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (43) (210 mg, 0.6 mmol) and DIEA (0.32 mL, 1.8 mmol) in DCM (5 mL) was added MsCl (138 mg, 1.2 mmol). The mixture was stirred at room temperature for 10 minutes then subjected to standard aqueous work up. The crude product was purified by silica chromatography to yield (3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methyl methanesulfonate (44) (180 mg, 70% yield). MS m/z 428.1 (M+1)<sup>+</sup>.

[0446] The following compounds were prepared according to the protocol described for (3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methyl methanesulfonate (44).

Intermediate number	Structure	Physical Data
44a		MS m/z 442.1 (M + 1) <sup>+</sup> .
44b		MS m/z 442.1 (M + 1) <sup>+</sup> .

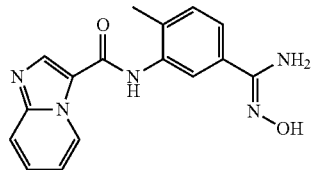
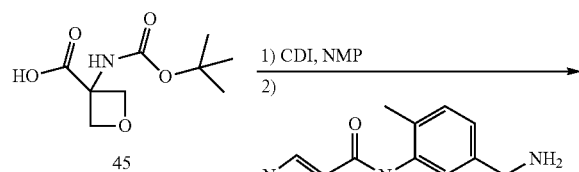
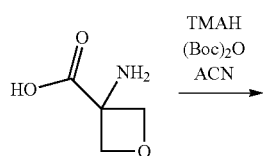
(crude used without isolation)

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Intermediate number	Structure	Physical Data
44c		MS m/z 432.1 (M + 1) <sup>+</sup> .
	(crude used without isolation)	
44d		MS m/z 446.1 (M + 1) <sup>+</sup> .

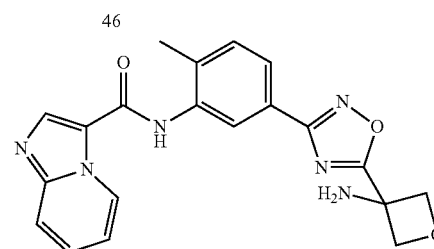
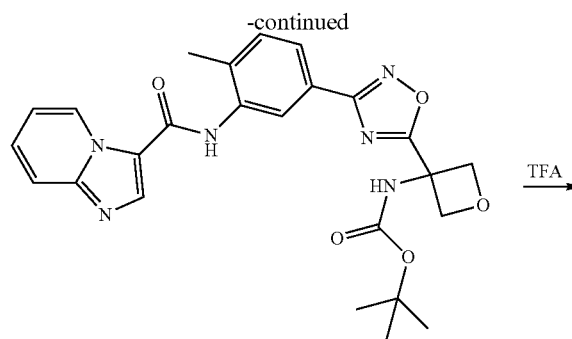
Synthesis of N-(5-(5-(3-aminooxetan-3-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (47)

[0447]



9

MW 125° C.



47

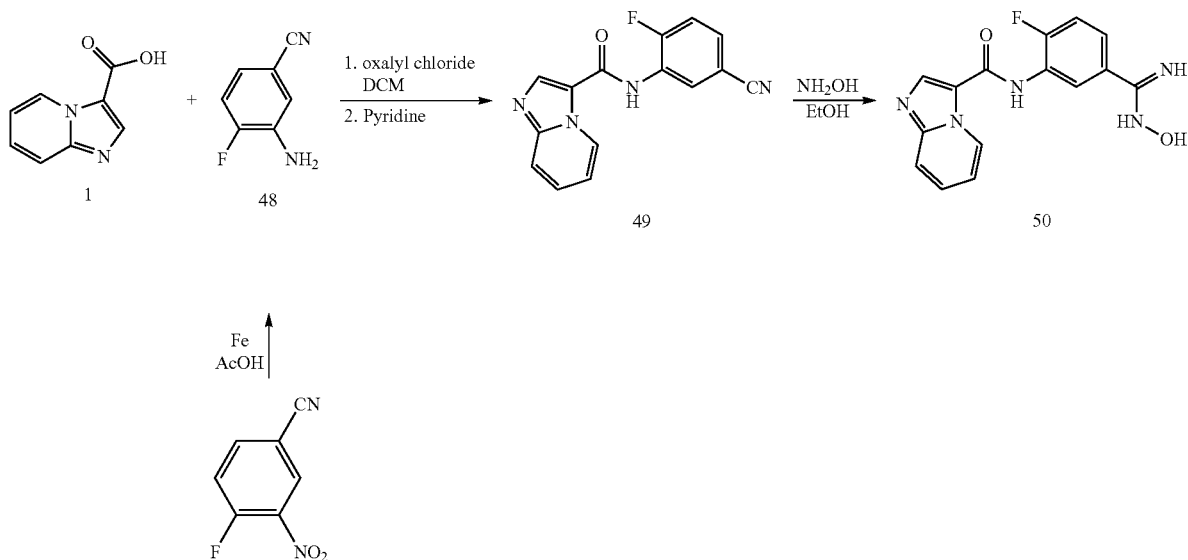
**[0448]** A mixture of 3-aminooxetan-3-carboxylic acid (117.0 mg, 1.0 mmol) and  $\text{NMe}_4\text{OH}\cdot 5\text{H}_2\text{O}$  (TMAH) (181.0 mg, 1.0 mmol) in  $\text{CH}_3\text{CN}$  (10 mL) was stirred at room temperature for 30 minutes. Then  $(\text{Boc})_2\text{O}$  (327.3 mg, 1.5 mmol) was added and the resulting mixture was stirred overnight. Water (10 mL) was added and the mixture was extracted with ether (20 mL). The aqueous layer was acidified to pH=2 by addition of citric acid (solid) and extracted with EtOAc (2×20 mL). The organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to yield crude 3-((tert-butoxycarbonyl)amino)oxetan-3-carboxylic acid (45) which was used

without further purification. MS  $m/z$  218.1 (M+1)<sup>+</sup>. Carbonyl diimidazole (CDI) (162.2 mg, 1.0 mmol) was added to a stirred solution of 3-((tert-butoxycarbonyl)amino)oxetane-3-carboxylic acid (45) (217.1 mg, 1.0 mmol) in NMP (1.0 mL). After 20 minutes, N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9) (150.0 mg, 0.5 mmol) was added in one portion and the resulting solution was stirred for 1 hour before it was heated at 125° C. for 15 minutes in a microwave reactor. The reaction solution was subjected to standard aqueous work up to afford a residue which was purified by silica chromatography to yield tert-butyl (3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)oxetan-3-yl)carbamate (46) (159 mg, 65% yield). MS  $m/z$  491.2 (M+1)<sup>+</sup>.

**[0449]** 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)oxetan-3-yl)carbamate (46) (29.5 mg, 0.06 mmol) was dissolved in TFA (0.5 mL) and stirred at room temperature for 10 minutes. Then TFA was removed under vacuum to yield crude N-(5-(5-(3-aminooxetan-3-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (47) as a TFA salt which was used without further purification. MS  $m/z$  391.1 (M+1)<sup>+</sup>.

Synthesis of N-(2-fluoro-5-(N'-hydroxycarbamimidoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (50)

**[0450]**



**[0451]** A mixture of 4-fluoro-3-nitrobenzonitrile (5.0 g, 30.1 mmol) and Fe powder (5.05 g, 90.3 mmol) in AcOH (100 mL) was heated at 80° C. for 1 hour under N<sub>2</sub>. Then the solvent was removed under vacuum and water (200 mL) was added to the residue. The solution was adjusted to pH 6 by addition of Na<sub>2</sub>CO<sub>3</sub> and extracted with DCM (2×200 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to yield 3-amino-4-fluorobenzonitrile

(48), which was used without further purification. MS  $m/z$  137.0 (M+1)<sup>+</sup>.

**[0452]** To a stirring suspension of imidazo[1,2-a]pyridine-3-carboxylic acid (1) (3.0 g, 18.5 mmol) in anhydrous dichloromethane (50 mL) at 0° C. was added dropwise oxalyl chloride (4.84 mL, 55.5 mmol). Then, three drops of anhydrous DMF was added and the reaction mixture was stirred at room temperature for 15 minutes. The solvent was concentrated and the crude solid was added to a stirring solution of 3-amino-4-fluorobenzonitrile (48) (2.5 g, 18.5 mmol) in anhydrous pyridine (50 mL) at room temperature. The reaction was stirred for 20 minutes and quenched with water (200 mL) with stirring for another 10 minutes. Then the precipitate was filtered and dried in air to yield N-(5-(5-(3-amino-2-fluorophenyl)imidazo[1,2-a]pyridine-3-carboxamide (49). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.40 (s, 1H), 9.43 (td, J=1.2, 6.8 Hz, 1H), 8.63 (s, 1H), 8.21 (dd, J=2.0, 7.2 Hz, 1H), 7.78-7.84 (m, 2H), 7.54-7.63 (m, 2H), 7.22 (dt, J=1.2, 6.8, 1H). MS  $m/z$  281.1 (M+1)<sup>+</sup>.

**[0453]** NH<sub>2</sub>OH (10 mL, 32.1 mmol) was added in one portion to a stirred suspension of N-(5-(5-(3-amino-2-fluorophenyl)imidazo[1,2-a]pyridine-3-carboxamide (49) (3.6 g, 12.85 mmol) in EtOH (100 mL). The resulting suspension was heated at 70° C. for 3 hours and then the solvent was removed to yield N-(2-fluoro-5-(N'-hydroxycarbamimidoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (50). <sup>1</sup>H

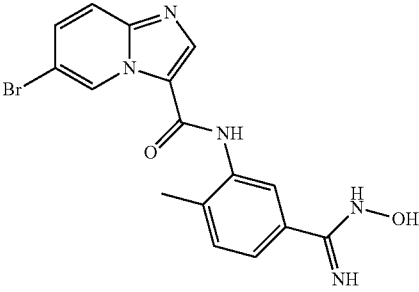
NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.21 (s, 1H), 9.70 (s, 1H), 9.45 (td, J=1.2, 7.2 Hz, 1H), 8.61 (s, 1H), 7.95 (dd, J=2.4, 7.6 Hz, 1H), 7.79 (td, J=1.2, 8.8 Hz, 1H), 7.51-7.60 (m, 2H), 7.31-7.37 (m, 1H), 7.19 (dt, J=1.2, 6.8, 1H), 5.88 (s, 2H). MS  $m/z$  314.1 (M+1)<sup>+</sup>.

**[0454]** The following compounds were prepared according to the protocol described for N-(2-fluoro-5-(N'-hydroxycarbamimidoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (50).



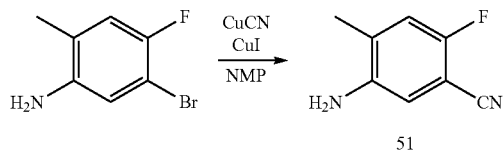
Intermediate number	Structure	Physical Data
50a		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) δ 9.96 (s, 1H), 9.65 (s, 1H), 9.44 (td, J = 0.8, 6.8 Hz, 1H), 8.55 (s, 1H), 7.78 (td, J = 1.2, 9.2 Hz, 1H), 7.52 (m, 2H), 7.21 (d, J = 11.6 Hz, 1H), 7.17 (dt, J = 1.2, 6.8, 1H), 5.81 (s, 2H), 2.28 (s, 3H). MS m/z 328.1 (M + 1) <sup>+</sup> .
50b		MS m/z 422.1 (M + 1) <sup>+</sup> .
50c		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) δ 9.89 (s, 1H), 9.44 (dt, J = 6.8, 1.2 Hz, 1H), 9.33 (s, 1H), 8.55 (s, 1H), 7.76 (dt, J = 9.2, 1.2 Hz, 1H), 7.49-7.52 (m, 1H), 7.28 (s, 1H), 7.14-7.18 (m, 2H), 5.72 (s, 2H), 2.34 (s, 3H), 2.24 (s, 3H). MS m/z 324.1 (M + 1) <sup>+</sup> .
50d		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) δ 9.84 (s, 1H), 9.43 (d, J = 6.8 Hz, 1H), 8.59 (s, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.17 (m, 3H), 5.76 (s, 2H), 2.25 (s, 3H), 2.24 (s, 3H). MS m/z 324.1 (M + 1) <sup>+</sup> .
50e		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) δ 9.90 (s, 1H), 9.60 (s, 1H), 9.32 (d, J = 7.2 Hz, 1H), 8.50 (s, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.56 (m, 1H), 7.50 (dd, J = 1.6, 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.02 (dd, J = 1.6, 7.2 Hz, 1H), 5.80 (s, 2H), 2.42 (s, 3H), 2.27 (s, 3H). MS m/z 324.1 (M + 1) <sup>+</sup> .

-continued

Intermediate number	Structure	Physical Data
50f		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.09 (s, 1H), 9.63 (m, 1H), 9.60 (s, 1H), 8.58 (s, 1H), 7.78 (dd, $J = 0.8, 9.6$ Hz, 1H), 7.69 (d, $J = 1.6$ Hz, 1H), 7.66 (dd, $J = 2.0, 9.2$ Hz, 1H), 7.52 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.31 (d, $J = 8.0$ Hz, 1H), 5.81 (s, 2H), 2.27 (s, 3H). MS $m/z$ 388.0, 390.0 ( $M + 1$ ) $^+$ .

Synthesis of 5-amino-2-fluoro-4-methylbenzonitrile (51)

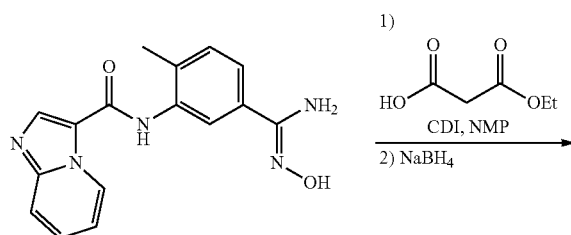
[0455]



[0456] A mixture of 5-bromo-4-fluoro-2-methylaniline (2.04 g, 10.0 mmol), CuCN (889 mg, 10.0 mmol) and CuI (1.9 g, 10.0 mmol) in NMP was purged with  $\text{N}_2$  for 5 minutes and then sealed and heated at  $195^\circ\text{C}$ . for 30 minutes under microwave condition. The mixture was subjected to standard aqueous workup to give a residue which was purified by silica chromatography to yield 5-amino-2-fluoro-4-methylbenzonitrile (51) (540 mg, 36% yield). MS  $m/z$  151.0 ( $M+1$ ) $^+$ .

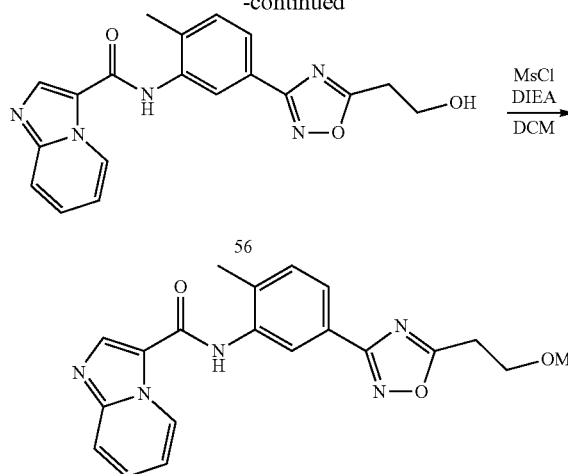
Synthesis of 2-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl) ethyl methanesulfonate (57)

[0457]



9

-continued



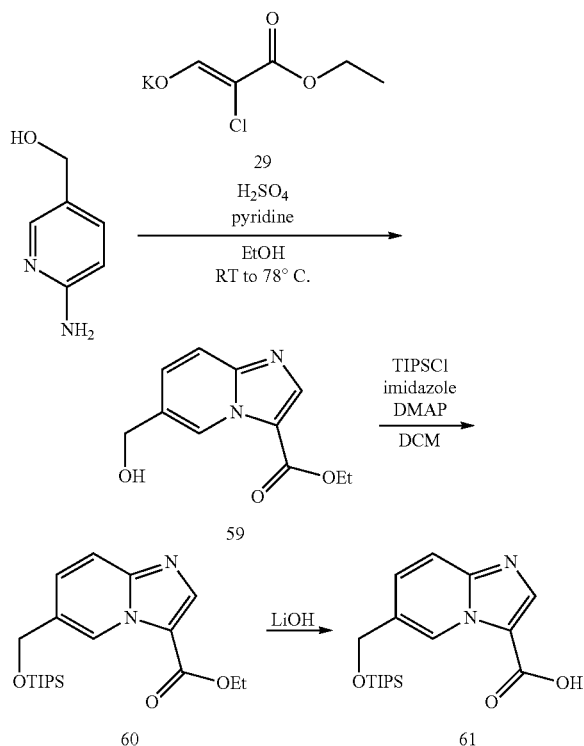
[0458] Carbonyl diimidazole (CDI) (233.3 mg, 1.44 mmol) was added to a stirred solution of 3-ethoxy-3-oxopropanoic acid (190.0 mg, 1.44 mmol) in NMP (1.0 mL). After 20 minutes, N-(5-(N-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9) (99.0 mg, 0.32 mmol) was added in one portion and the resulting solution was stirred for 30 minutes before it was heated at  $125^\circ\text{C}$ . for 15 minutes in a microwave reactor. The reaction mixture was added to water (20 mL) and extracted with EtOAc. The organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to afford a residue which was dissolved in MeOH (1 mL).  $\text{NaBH}_4$  (122.0 mg, 3.2 mmol) was added to the above solution slowly and the resulting mixture was stirred at room temperature for 30 minutes. The mixture was subjected to standard aqueous workup to give crude N-(5-(5-(2-hydroxyethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (56) which was used without further purification. MS  $m/z$  364.1 ( $M+1$ ) $^+$ .

[0459] To a solution of crude N-(5-(5-(2-hydroxyethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (56) and DIEA (0.11 mL, 0.64 mmol) in dichloromethane (5 mL) was added MsCl (55.0 mg, 0.48 mmol). The resulting mixture was stirred at room temperature for 10 minutes. Then the mixture was subjected to standard aqueous work up to afford crude 2-(3-(3-(imidazo[1,2-a]py-

ridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)ethyl methanesulfonate (57), which was used without purification. MS  $m/z$  442.1 (M+1)<sup>+</sup>.

Synthesis of 6-(((triisopropylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxylic acid (61)

[0460]



[0461] To a stirring suspension of (6-aminopyridin-3-yl) methanol (1.24 mg, 10.0 mmol) and ethyl 2-chloro-3-hydroxyacrylate, potassium salt (29) (3.76 g, 20.0 mmol) in EtOH (10 mL) at room temperature was added conc sulfuric acid (10.0 mmol) dropwise. The reaction mixture was stirred at room temperature for 15 minutes and pyridine (0.92 g, 12.0 mmol) was added. The resulting mixture was heated at 85° C. overnight. The reaction was cooled to room temperature and the solvent was concentrated. The residue was taken in water and the solution was adjusted to pH 8 with saturated sodium bicarbonate. The crude product was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The crude product ethyl 6-(hydroxymethyl)imidazo[1,2-a]pyridine-3-carboxylate (59) was purified by silica chromatography. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO) δ 9.16 (d, J=6.8 Hz, 1H), 8.26 (s, 1H), 7.67 (s, 1H), 7.19 (dd, J=1.6, 6.8 Hz, 1H), 5.57 (t, J=6.4 Hz, 1H), 4.63 (d, J=6.0, 2H), 4.36 (q, J=7.2 Hz, 2H), 1.35 (t, J=6.8 Hz, 3H). MS  $m/z$  221.1 (M+1)<sup>+</sup>.

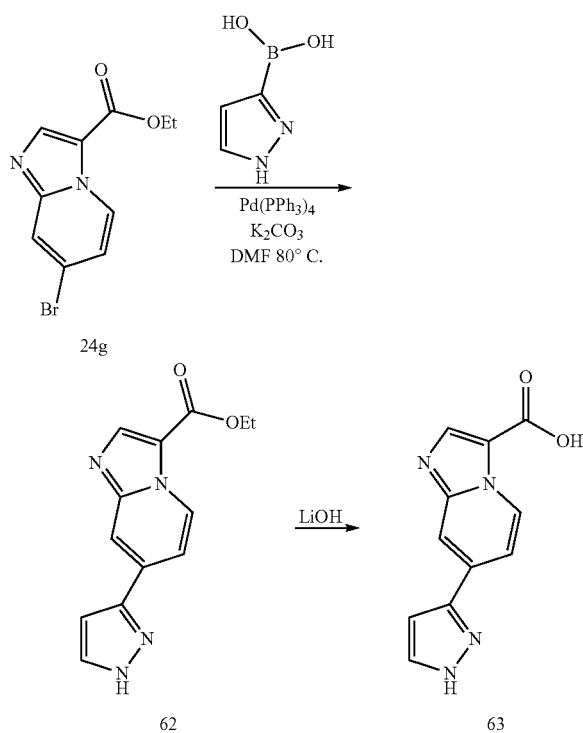
[0462] To a suspension of ethyl 6-(hydroxymethyl)imidazo[1,2-a]pyridine-3-carboxylate (59) (497.0 mg, 2.26 mmol), DMAP (12.2 mg, 0.1 mmol) and 1H-imidazole (154.0 mg, 2.26 mmol) in dichloromethane (10 mL), was added TIPSCl (523.0 mg, 2.71 mmol). The resulting mixture was stirred overnight at room temperature. The solvent was removed

under vacuum to yield crude ethyl 6-(((triisopropylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxylate (60). MS  $m/z$  377.2 (M+1)<sup>+</sup>.

[0463] The crude ethyl 6-(((triisopropylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxylate (60) obtained above was dissolved in THF/MeOH/H<sub>2</sub>O (3:2:1, 5 mL). 6N LiOH (2.27 mL, 13.6 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. All solvents were removed and 6N HCl was added until pH 5-6. EtOAc (5 mL) was added and the mixture was stirred for 1 hour. The precipitate was filtered and dried to give 6-(((triisopropylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxylic acid (61). <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO) δ 9.37 (s, 1H), 8.21 (s, 1H), 7.76 (dd, J=1.2, 9.2 Hz, 1H), 7.46 (dd, J=2.0, 9.2 Hz, 1H), 4.94 (s, 2H), 1.20 (m, 3H), 1.08 (d, J=6.8 Hz, 18H). MS  $m/z$  349.2 (M+1)<sup>+</sup>.

Synthesis of 7-(1H-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (63)

[0464]

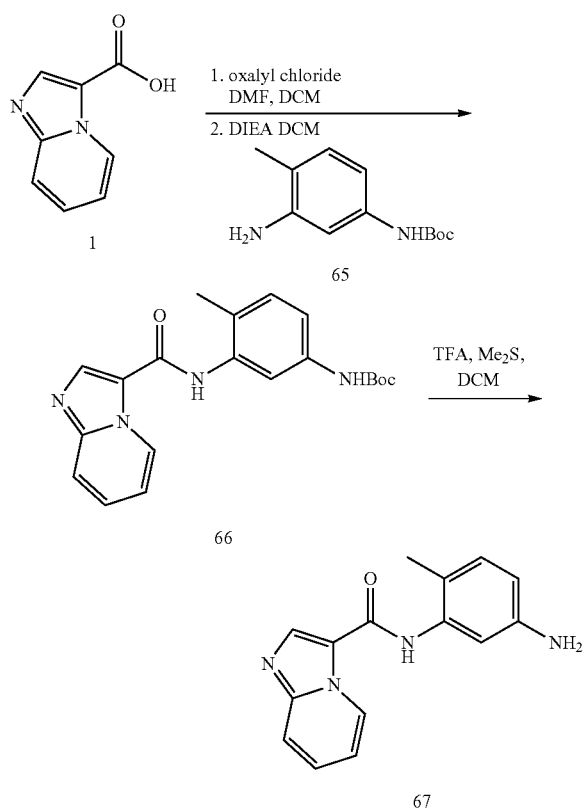


[0465] To a solution of 5-ethyl 7-bromoimidazo[1,2-a]pyridine-3-carboxylate (24g) (202 mg, 0.75 mmol) in DMF (2 mL) was added (1H-pyrazol-3-yl)boronic acid (101 mg, 0.903 mmol), 1.8 M K<sub>2</sub>CO<sub>3</sub> (1.3 mL, 2.26 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (87 mg, 0.075 mmol). The reaction was evacuated and backfilled with nitrogen twice then heated at 160° C. for 10 minutes in a microwave oven. After the reaction mixture was filtered through a pad of Celite, the mixture was diluted with a saturated solution of NH<sub>4</sub>Cl and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give ethyl 7-(1H-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxylate (62). MS ( $m/z$ ) 257.1 (M+1)<sup>+</sup>.

**[0466]** To a stirring solution of ethyl 7-(1H-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxylate (62) (103 mg, 0.4 mmol) in THF:MeOH:H<sub>2</sub>O (3:2:1, 1.6 mL) was added 6N LiOH (0.035 mL). The reaction was stirred at room temperature for 20 minutes. The pH was adjusted between 4-5 with 3N HCl. The resulting mixture was concentrated to yield 7-(1H-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (63). MS (m/z) 229.2 (M+1)<sup>+</sup>.

Synthesis of N-(5-amino-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (67)

**[0467]**

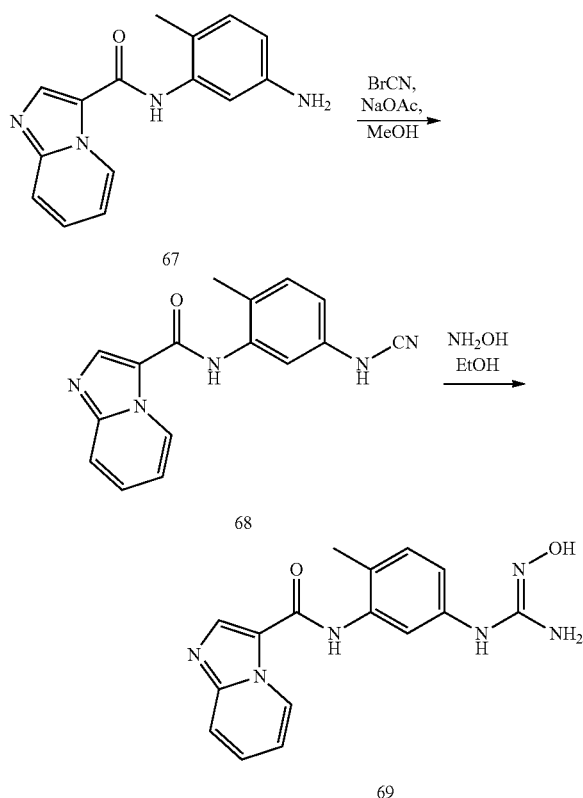


**[0468]** Oxalyl chloride (10 mL) was added dropwise to a stirred solution of imidazo[1,2-a]pyridine-3-carboxylic acid (1) (3 g, 18.5 mmol) in dry dichloromethane (100 mL) and a few drops of DMF. The resulting solution was stirred at room temperature for 5 hours before it was evaporated to dryness and fresh dichloromethane was added to the resulting acid chloride to make a suspension. In a separate flask, tert-butyl 3-amino-4-methylphenylcarbamate (65) (4.5 g, 20.3 mmol) and DIEA (10 mL) was dissolved in dichloromethane (100 mL) and the above acid chloride solution was added slowly. The resulting solution was stirred overnight at room temperature. Saturated NH<sub>4</sub>Cl was added to the reaction solution and the phases were separated. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. After evaporation, the residue was purified over silica gel column using hexane and EtOAc to give tert-butyl 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenylcarbamate (66) as a slightly yellow solid.

**[0469]** TFA (50 mL) was added to a stirred suspension of tert-butyl 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenylcarbamate (66) in Me<sub>2</sub>S (5 mL) and dichloromethane (10 mL). After 2 hours the solution was evaporated and partitioned with dichloromethane and saturated NaHCO<sub>3</sub>. The aqueous layer was extracted several times with dichloromethane and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. N-(5-amino-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (67) was isolated and used without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.44 (d, J=6.8 Hz, 1H), 8.05 (s, 1H), 7.67 (d, J=8.8 Hz, 1H), 7.38-7.33 (m, 2H), 6.98-6.94 (m, 2H), 2.19 (s, 3H). MS m/z 267.1 (M+1)<sup>+</sup>.

Synthesis of (E)-N-(5-(2-hydroxyquanidino)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (69)

**[0470]**



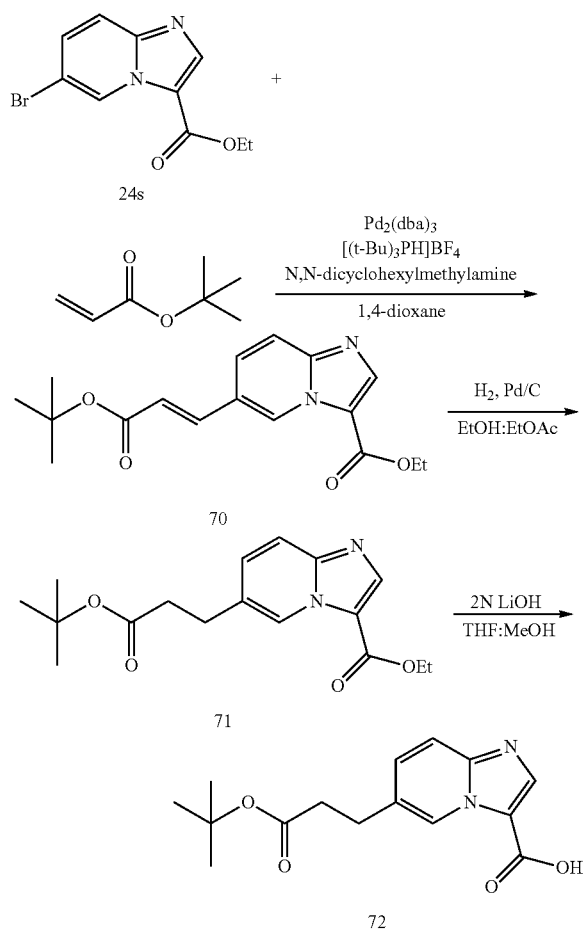
**[0471]** To N-(5-amino-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (67) (4.53 g, 15 mmol) in MeOH (100 mL) was added KOAc (4.41 g, 45 mmol) and the mixture was stirred at room temperature for 5 minutes then cooled to 0° C. before a solution of BrCN (1.62 g, 15 mmol) in MeOH (30 mL) was added dropwise. The resulting mixture was slowly warmed to room temperature and stirred overnight. The solvent was evaporated and to the residue was added water (150 mL). The mixture was stirred at room temperature for 1 hour, filtered and washed with water (2x20 mL), then air dried to give N-(5-cyanamido-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (68) as a white solid.

**[0472]** To a suspension of N-(5-cyanamido-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (68) 3.52 g (12.1

mmol) in 200 mL of EtOH was added 0.75 mL  $\text{NH}_2\text{OH}$  (50 wt % in water, 12.1 mmol). The resulting mixture was stirred at room temperature overnight. The precipitate was filtered, washed with EtOH (10 mL) and air dried to give N-(5-(2-hydroxyguanidino)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (69) as a white solid, which was used directly in the next step without further purification.  $^1\text{H NMR}$  (400 MHz,  $d_6$ -DMSO)  $\delta$  9.44 (s, 1H), 9.46 (dd,  $J=6.8, 0.8$  Hz, 1H), 8.54 (s, 1H), 8.34 (s, 1H), 7.76 (dd,  $J=7.2, 2.2$  Hz, 1H), 7.59 (s, 1H), 7.52-7.43 (m, 2H), 7.18-7.06 (m, 2H), 2.13 (s, 3H). MS  $m/z$  325.1 ( $M+1$ ) $^+$ .

Synthesis of 6-(3-(tert-butoxy)-3-oxobrom)imidazo[1,2-a]pyridine-3-carboxylic acid (72)

[0473]



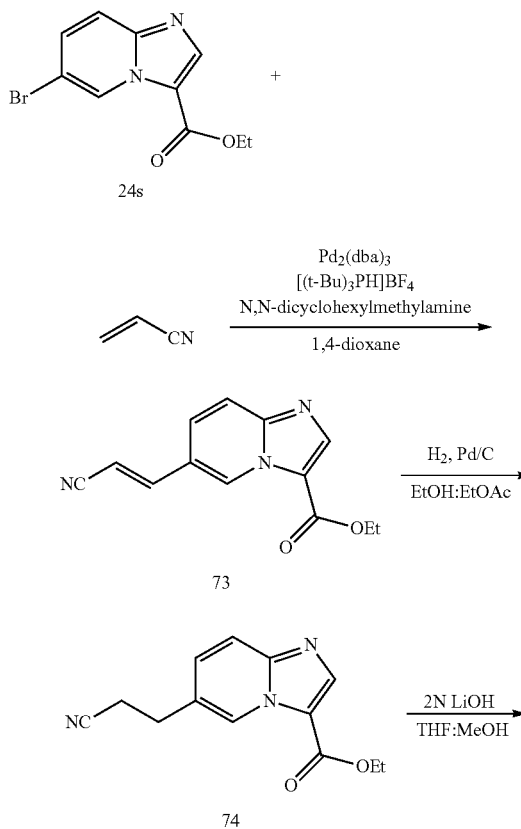
[0474] A stirring mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (24s) (500 mg, 1.86 mmol), tert-butyl acrylate (408  $\mu\text{L}$ , 2.79 mmol), tris(dibenzylideneacetone) dipalladium(0) (51 mg, 0.056 mmol),  $[(t\text{-Bu})_3\text{PH}]\text{BF}_4$  (27 mg, 0.093 mmol) and N,N-dicyclohexylmethylamine (738  $\mu\text{L}$ , 3.48 mmol) in anhydrous 1,4-dioxane (5 mL) was heated at 95 $^\circ$  C. overnight. The reaction was cooled to room temperature and filtered. The solvent was concentrated and the crude product was purified by silica chromatography to yield ethyl 6-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)imidazo[1,2-a]pyridine-3-carboxylate (70). MS  $m/z$  317.14 ( $M+1$ ) $^+$ .

[0475] A stirring mixture of ethyl 6-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)imidazo[1,2-a]pyridine-3-carboxylate (70) (460 mg, 1.80 mmol) and 10 wt % Pd/C (wet) in ethanol:ethylacetate (1:1, 10 mL) was hydrogenated overnight. The reaction was filtered over celite and the solvent was concentrated. Crude ethyl 6-(3-(tert-butoxy)-3-oxopropyl)imidazo[1,2-a]pyridine-3-carboxylate (71) was used in the next step without further purification. MS  $m/z$  319.16 ( $M+1$ ) $^+$ .

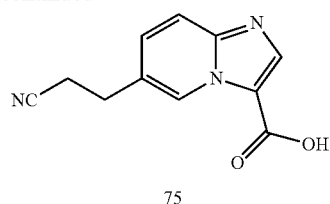
[0476] A stirring mixture of ethyl 6-(3-(tert-butoxy)-3-oxopropyl)imidazo[1,2-a]pyridine-3-carboxylate (71) (400 mg, 1.26 mmol) and 2N LiOH (1 mL) in THF:MeOH (4:1, 4 mL) was heated at 60 $^\circ$  C. for 30 minutes. The reaction was cooled to room temperature and the pH was adjusted between 3-5 with 10% citric acid. The solvent was partially reduced. The resulting solid was collected by vacuum filtration and washed with excess water. Crude 6-(3-(tert-butoxy)-3-oxopropyl)imidazo[1,2-a]pyridine-3-carboxylic acid (72) was dried and used in the next step without further purification.  $^1\text{H NMR}$  (400 MHz,  $d_6$ -DMSO)  $\delta$  9.11 (s, 1H), 8.20 (s, 1H), 7.72 (dd,  $J=0.8, 9.2$  Hz, 1H), 7.50 (dd,  $J=1.6, 9.2$  Hz, 1H), 2.91 (t,  $J=6.8$  Hz, 2H), 2.60 (t,  $J=7.2, 2$  H), 1.33 (s, 9H). MS  $m/z$  291.13 ( $M+1$ ) $^+$ .

Synthesis of 6-(2-cyanoethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (75)

[0477]



-continued

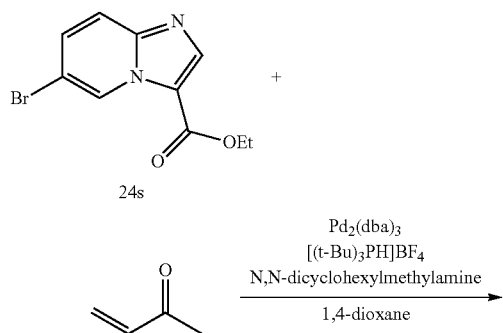


**[0478]** A stirring mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (24s) (250 mg, 0.929 mmol), acrylonitrile (92  $\mu$ L, 1.39 mmol), tris(dibenzylideneacetone) dipalladium(0) (26 mg, 0.0279 mmol), [(t-Bu)<sub>3</sub>PH]BF<sub>4</sub> (13 mg, 0.0465 mmol) and N,N-dicyclohexylmethylamine (217  $\mu$ L, 1.02 mmol) in anhydrous 1,4-dioxane (4 mL) was heated at 95° C. overnight. The reaction was cooled to room temperature and filtered. The solvent was concentrated and crude 6-(2-cyanovinyl)imidazo[1,2-a]pyridine-3-carboxylate (73) was purified by silica chromatography. MS m/z 242.09 (M+1)<sup>+</sup>.

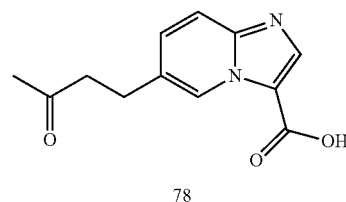
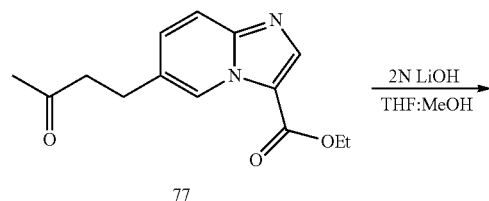
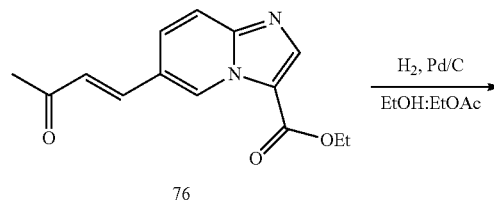
**[0479]** A stirring mixture of ethyl 6-(2-cyanovinyl)imidazo[1,2-a]pyridine-3-carboxylate (73) (115 mg, 0.451 mmol) and 10 wt % Pd/C (wet) in ethanol:ethylacetate (1:1, 5 mL) was hydrogenated overnight. The reaction was filtered over celite and the solvent was removed. Crude ethyl 6-(2-cyanoethyl)imidazo[1,2-a]pyridine-3-carboxylate (74) was used in the next step without further purification. MS m/z 244.10 (M+1)<sup>+</sup>.

**[0480]** A stirring mixture of ethyl 6-(2-cyanoethyl)imidazo[1,2-a]pyridine-3-carboxylate (74) (100 mg, 0.411 mmol) and 2N LiOH (0.2 mL) in THF:MeOH (4:1, 3 mL) was heated at 50° C. for 45 minutes. The reaction was cooled to room temperature and the pH was adjusted between 3-5 with 10% citric acid. The solvent was partially reduced. The resulting solid was collected by vacuum filtration and washed with excess water. Crude 6-(2-cyanoethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (75) was dried and used in the next step without further purification. MS m/z 416.07 (M+1)<sup>+</sup>.

Synthesis of  
6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic  
acid (78)

**[0481]**

-continued



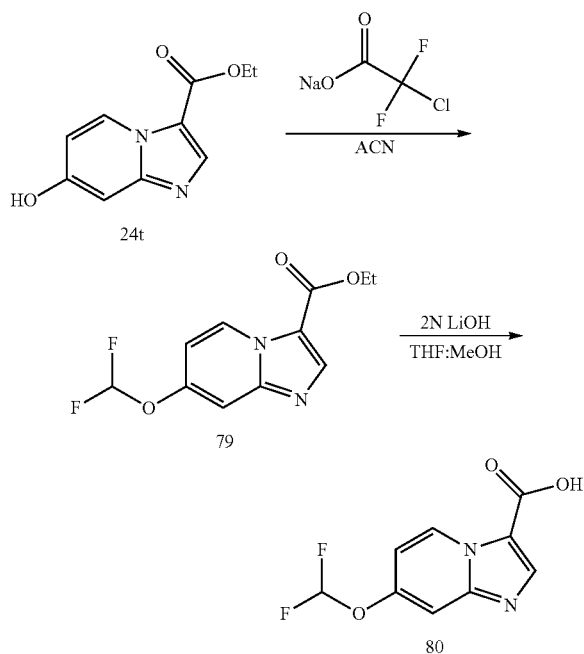
**[0482]** A stirring mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (24s) (250 mg, 0.929 mmol), methyl vinyl ketone (151  $\mu$ L, 1.86 mmol), tris(dibenzylideneacetone)dipalladium(0) (26 mg, 0.0279 mmol), [(t-Bu)<sub>3</sub>PH]BF<sub>4</sub> (13 mg, 0.0465 mmol) and N,N-dicyclohexylmethylamine (217  $\mu$ L, 1.02 mmol) in anhydrous 1,4-dioxane (4 mL) was heated at 95° C. overnight. The reaction was cooled to room temperature and filtered. The solvent was concentrated and crude 6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylate (76) was purified by silica chromatography. MS m/z 259.10 (M+1)<sup>+</sup>.

**[0483]** A stirring mixture of ethyl 6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylate (76) (200 mg, 0.774 mmol) and 10 wt % Pd/C (wet) in ethanol:ethylacetate (1:1, 8 mL) was hydrogenated overnight. The reaction was filtered over celite and the solvent was concentrated. Crude 6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylate (77) was used in the next step without further purification. MS m/z 261.12 (M+1)<sup>+</sup>.

**[0484]** A stirring mixture of ethyl 6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylate (77) (190 mg, 0.730 mmol) and 2N LiOH (0.2 mL) in THF:MeOH (4:1, 3 mL) was heated at 50° C. for 45 minutes. The reaction was cooled to room temperature and the pH was adjusted between 3-5 with 10% citric acid. The solvent was partially reduced. The resulting solid was collected by vacuum filtration and washed with excess water. Crude 6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic acid (78) was dried and used in the next step without further purification. MS m/z 233.08 (M+1)<sup>+</sup>.

Synthesis of  
6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic  
acid (80)

[0485]

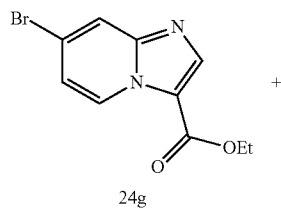


**[0486]** A mixture of ethyl 7-hydroxyimidazo[1,2-a]pyridine-3-carboxylate (24t) (500 mg, 2.43 mmol) and sodium chlorodifluoroacetate (444 mg, 2.91 mmol) in anhydrous acetonitrile (8 mL) was heated in the microwave at 125° C. for 12 minutes. The solvent was concentrated and the crude product ethyl 7-(difluoromethoxy)imidazo[1,2-a]pyridine-3-carboxylate (79) was purified by silica chromatography. MS *m/z* 257.07 (M+1)<sup>+</sup>.

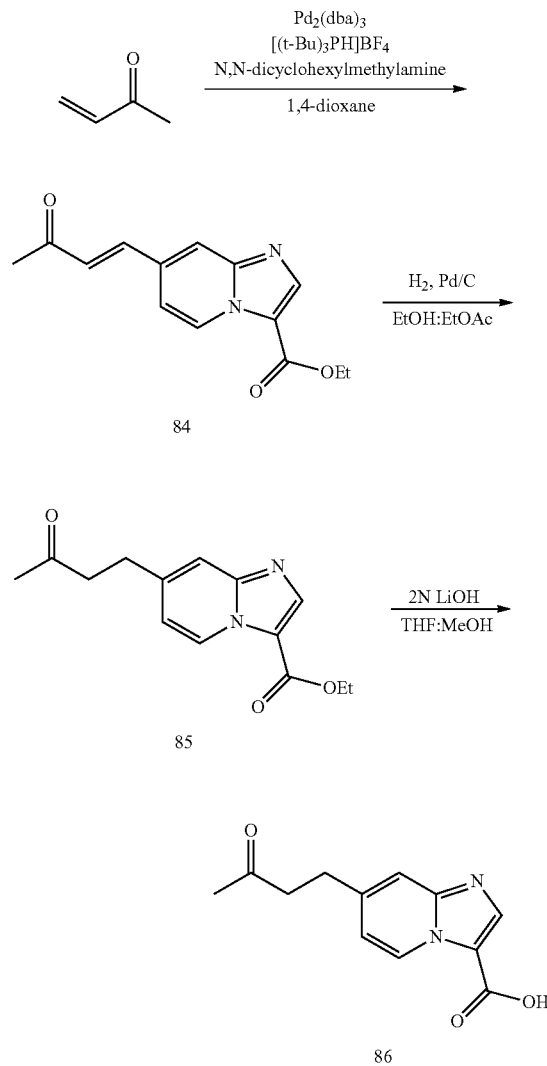
**[0487]** A stirring mixture of ethyl 7-(difluoromethoxy)imidazo[1,2-a]pyridine-3-carboxylate (79) (150 mg, 0.585 mmol) and 2N LiOH (1 mL) in THF:MeOH (4:1, 5 mL) was heated at 60° C. for 45 minutes. The reaction was cooled to room temperature and the pH was adjusted between 4-5 with 1N HCl. The solvent was partially reduced and the crude product was purified by reverse phase preparative HPLC to yield 6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic acid (80). MS *m/z* 229.03 (M+1)<sup>+</sup>.

Synthesis of  
7-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic  
acid (86)

[0488]



-continued



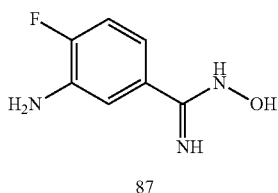
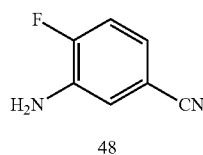
**[0489]** A stirring mixture of ethyl 7-bromoimidazo[1,2-a]pyridine-3-carboxylate (24g) (500 mg, 1.86 mmol), methyl vinyl ketone (301  $\mu$ L, 3.72 mmol), tris(dibenzylideneacetone)dipalladium(0) (51 mg, 0.056 mmol), [(t-Bu)<sub>3</sub>PH]BF<sub>4</sub> (27 mg, 0.093 mmol) and N,N-dicyclohexylmethylamine (433  $\mu$ L, 2.04 mmol) in anhydrous 1,4-dioxane (10 mL) was heated at 95° C. overnight. The reaction was cooled to room temperature and filtered. The solvent was concentrated and crude ethyl 7-(3-oxobut-1-enyl)imidazo[1,2-a]pyridine-3-carboxylate (84) was purified by silica chromatography. MS *m/z* 259.10 (M+1)<sup>+</sup>.

**[0490]** A stirring mixture of ethyl 7-(3-oxobut-1-enyl)imidazo[1,2-a]pyridine-3-carboxylate (84) (92 mg, 0.356 mmol) and 10 wt % Pd/C (wet) in ethanol:ethylacetate (1:1, 8 mL) was hydrogenated overnight. The reaction was filtered over celite and the solvent was concentrated. Crude ethyl 7-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylate (85) was used in the next step without further purification. MS *m/z* 261.12 (M+1)<sup>+</sup>.

**[0491]** A stirring mixture of ethyl 7-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylate (85) (90 mg, 0.346 mmol) and 2N LiOH (0.5 mL) in THF:MeOH (4:1, 3 mL) was heated at 60° C. for 45 minutes. The reaction was cooled to room temperature and the pH was adjusted between 3-5 with 10% citric acid. The solvent was partially concentrated and the crude product was purified by reverse phase preparative HPLC to yield 7-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic acid (86). MS m/z 233.08 (M+1)<sup>+</sup>.

Synthesis of  
3-amino-4-fluoro-N-hydroxybenzimidamide (87)

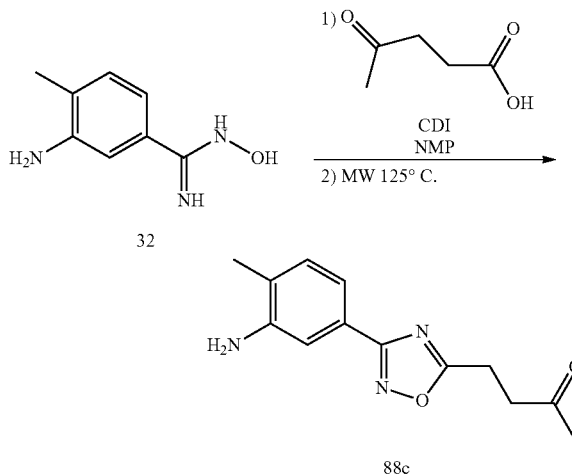
**[0492]**



**[0493]**  $\text{NH}_2\text{OH}$  (50% wt in water, 3.5 mL, 60.0 mmol) was added in one portion to a stirred suspension of 3-amino-4-fluorobenzonitrile (48) (1.36 g, 10.0 mmol) in EtOH (25 mL). The resulting suspension was heated at 70° C. for overnight and then the solvent was removed to yield 3-amino-4-fluoro-N-hydroxybenzimidamide (87) in a quantitative yield. MS m/z 170.1 (M+1)<sup>+</sup>.

Synthesis of 4-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)butan-2-one (88c)

**[0494]**



**[0495]** To a solution of 4-oxopentanoic acid (0.46 g, 4.0 mmol) in NMP (15 mL) was slowly added CDI (0.65 g, 4 mmol). The resulting mixture was stirred at room temperature for 30 minutes. Then 3-amino-N-hydroxy-4-methylbenzimidamide (32) (0.33 g, 2.0 mmol) was added and stirred for another 30 minutes. LCMS showed the coupling reaction was completed and then the reaction mixture was heated at 125° C. for 15 minutes via microwave. The reaction mixture was poured into water (100 mL), extracted with EtOAc (2×50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The crude product was purified by silica-gel chromatography (0-100% EtOAc in hexanes) to afford 4-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)butan-2-one (88c).  $^1\text{H NMR}$  (400 MHz,  $d_6$ -DMSO)  $\delta$  7.27 (d,  $J=1.6$  Hz, 1H), 7.07 (m, 2H), 5.17 (s, 2H), 3.08 (m, 4H), 2.18 (s, 3H), 2.10 (s, 3H). MS m/z 246.1 (M+1)<sup>+</sup>.

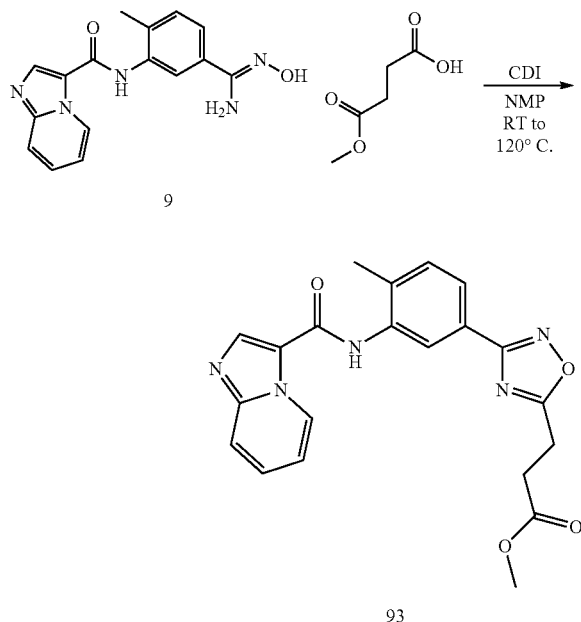
**[0496]** The following compounds were prepared according to the protocol described for 4-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)butan-2-one (88c).

Intermediate number	Structure	Physical Data
88a		$^1\text{H NMR}$ (400 MHz, $\text{CDCl}_3$ ) $\delta$ 7.55 (dd, $J = 2.4, 8.4$ Hz, 1H), 7.43-7.48 (m, 1H), 7.10 (dd, $J = 10.8, 8.4$ Hz, 1H), 4.89 (s, 2H), 3.88 (br, 2H), 3.84-3.87 (m, 2H), 3.64-3.67 (m, 2H), 3.42 (s, 3H). MS m/z 268.1 (M+1) <sup>+</sup> .
88b		$^1\text{H NMR}$ (400 MHz, $\text{CDCl}_3$ ) $\delta$ 7.49 (dd, $J = 2.0, 8.8$ Hz, 1H), 7.42 (m, 1H), 7.08 (dd, $J = 10.8, 8.4$ Hz, 1H), 3.87 (s, 2H), 3.20 (m, 2H), 3.08 (m, 2H), 2.82 (s, 3H). MS m/z 250.1 (M+1) <sup>+</sup> .



Synthesis of methyl 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)propanoate (93)

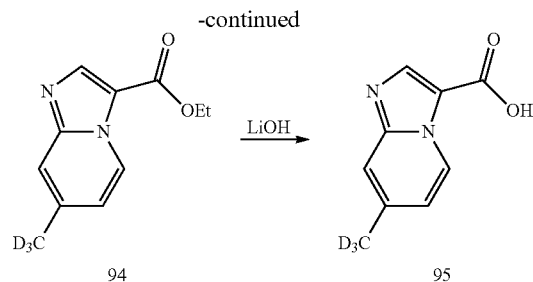
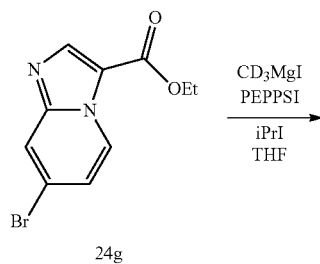
[0497]



[0498] To a stirring solution of 4-methoxy-4-oxobutanoic acid (256 mg, 1.94 mmol) in anhydrous NMP (3 mL) was added CDI (315 mg, 1.94 mmol). The reaction was stirred for 2 minutes. N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9) (300 mg, 0.97 mmol) was added and the reaction was stirred for 15 minutes followed by heating in a microwave at 120° C. for 15 minutes. The crude was purified over silica gel using 10% MeOH in dichloromethane to give methyl 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)propanoate (93).

Synthesis of 7-methyl-d<sub>3</sub>-imidazo[1,2-a]pyridine-3-carboxylic acid 95

[0499]

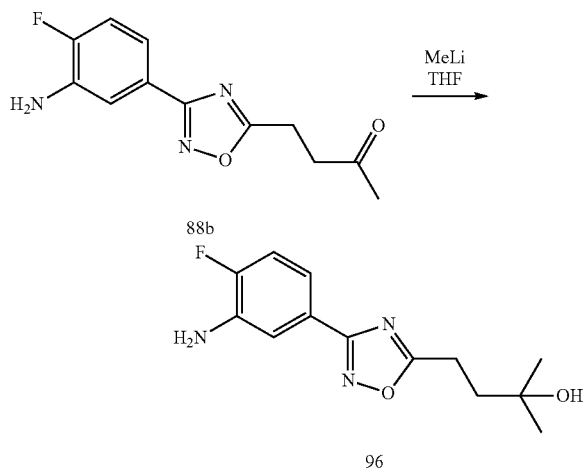


[0500] To a stirring solution of ethyl 7-bromoimidazo[1,2-a]pyridine-3-carboxylate (24g) (500 mg, 1.86 mmol), PEPPSI (63.2 mg, 0.093 mmol) and 2-iodopropane (928 uL, 9.3 mmol) in anhydrous THF (3 mL) at 0° C. under a stream of nitrogen was added methyl-d<sub>3</sub>-magnesium iodide (5.6 mL, 5.57 mmol). The reaction was stirred to room temperature for 5 hours. Then, the reaction was quenched with NH<sub>4</sub>Cl. The crude product was extracted with ether, washed with water and brine and dried over sodium sulfate. The product was purified on silica gel using 10% MeOH in dichloromethane to yield ethyl 7-methyl-d<sub>3</sub>-imidazo[1,2-a]pyridine-3-carboxylate (94). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 8.85 (dd, J=0.4, 7.0 Hz, 1H), 7.98 (s, 1H), 7.36 (s, 1H), 6.86 (dd, J=1.6, 7.2 Hz, 1H), 4.10 (q, J=7.2 Hz, 2H), 1.09 (t, J=7.2 Hz, 3H). MS m/z 208.1 (M+1)<sup>+</sup>.

[0501] To a stirring suspension of ethyl 7-methyl-d<sub>3</sub>-imidazo[1,2-a]pyridine-3-carboxylate (94) (142 mg, 0.69 mmol) in THF: MeOH: H<sub>2</sub>O (3:2:1, 3 mL) was added 6N LiOH (0.34 mL). The reaction was stirred at room temperature for 2 hours then neutralized with sodium bisulfate monohydrate and concentrated to afford 7-methyl-d<sub>3</sub>-imidazo[1,2-a]pyridine-3-carboxylic acid (95), which was immediately used without purification. MS (m/z) 180.1 (M+1)<sup>+</sup>.

Synthesis of 4-(3-(3-amino-4-fluorophenyl)-1,2,4-oxadiazol-5-yl)-2-methylbutan-2-ol (96)

[0502]

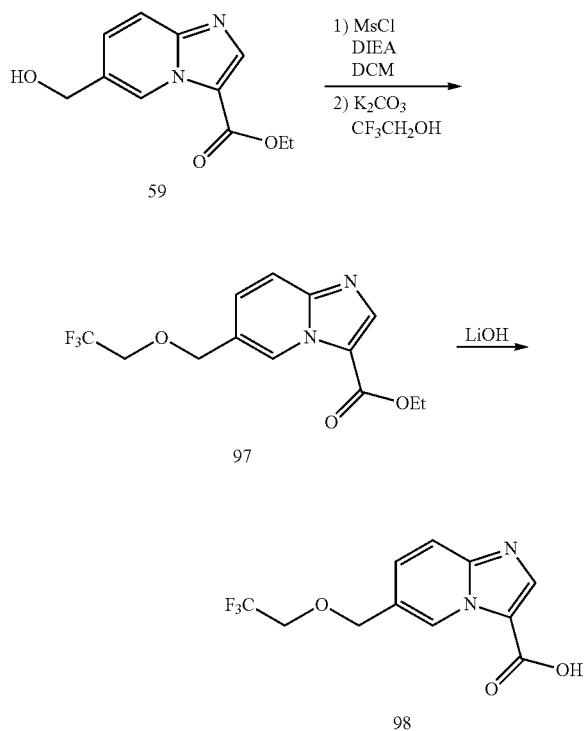


[0503] To a stirring solution of 4-(3-(3-amino-4-fluorophenyl)-1,2,4-oxadiazol-5-yl)butan-2-one (88b) (77 mg, 0.31 mmol) in anhydrous THF at -78° C. was added dropwise a

solution of methyllithium (37.2 mmol). The reaction was stirred at room temperature for 30 minutes. The reaction was cooled to 0° C. and quenched with water. The crude product was extracted with ethyl acetate and dried over sodium sulfate. The product was purified by silica chromatography to yield 4-(3-(3-amino-4-fluorophenyl)-1,2,4-oxadiazol-5-yl)-2-methylbutan-2-ol (96). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.51 (dd, J=2.0, 8.4 Hz, 1H), 7.44 (m, 1H), 7.09 (dd, J=10.8, 8.4 Hz, 1H), 3.87 (s, 2H), 3.09 (m, 2H), 2.08 (m, 2H), 1.34 (s, 6H). MS m/z 266.1 (M+1)<sup>+</sup>.

Synthesis of 6-(2,2,2-trifluoroethoxy)methylimidazo[1,2-a]pyridine-3-carboxylic acid (98)

[0504]



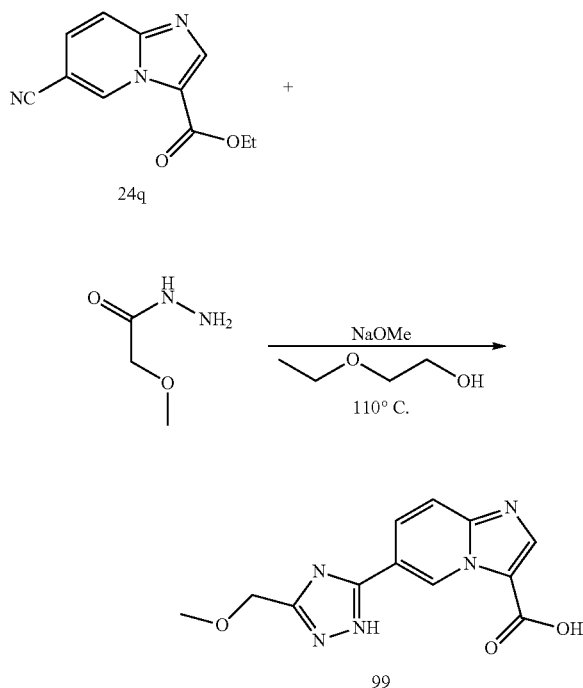
[0505] To a solution of ethyl 6-(hydroxymethyl)imidazo[1,2-a]pyridine-3-carboxylate (59) (460 mg, 2.2 mmol) and DIEA (0.78 mL, 4.4 mmol) in DCM (5 mL) was added MsCl (303 mg, 2.64 mmol). The mixture was stirred at room temperature for 10 minutes then subjected to standard aqueous work up to give a residue. The crude product was dissolved in 2,2,2-trifluoroethanol (2 mL) and was added K<sub>2</sub>CO<sub>3</sub> (608 mg, 4.4 mmol). The reaction mixture was heated at 80° C. for 2 hours. Once complete, the reaction mixture was diluted and extracted with EtOAc. The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford a residue which was purified by silica chromatography to yield ethyl 6-((2,2,2-trifluoroethoxy)methyl)imidazo[1,2-a]pyridine-3-carboxylate (97). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.33 (m, 1H), 8.32 (s, 1H), 7.76 (dd, J=0.8, 9.2 Hz, 1H), 7.47 (dd,

J=2.0, 9.2 Hz, 1H), 4.76 (s, 2H), 4.44 (q, J=7.2 Hz, 2H), 3.92 (q, J=8.4 Hz, 2H), 1.45 (t, J=7.2 Hz, 3H). MS m/z 303.1 (M+1)<sup>+</sup>.

[0506] A solution of ethyl 6-((2,2,2-trifluoroethoxy)methyl)imidazo[1,2-a]pyridine-3-carboxylate (97) (280 mg, 0.92 mmol) in THF/MeOH/H<sub>2</sub>O (3:2:1, 5 mL) was treated with 6N LiOH (0.92 mL, 5.52 mmol) and stirred at room temperature for 1 hour. All solvents were removed and 6N HCl was added to adjust pH 5-6. Then the mixture was purified by HPLC to give 6-((2,2,2-trifluoroethoxy)methyl)imidazo[1,2-a]pyridine-3-carboxylic acid (98). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 9.34 (m, 1H), 8.40 (s, 1H), 7.88 (dd, J=0.8, 9.2 Hz, 1H), 7.65 (dd, J=1.6, 9.2 Hz, 1H), 4.83 (s, 2H), 4.18 (q, J=9.6 Hz, 2H). MS m/z 275.1 (M+1)<sup>+</sup>.

Synthesis of 6-(3-(methoxymethyl)-1H-1,2,4-triazol-5-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (99)

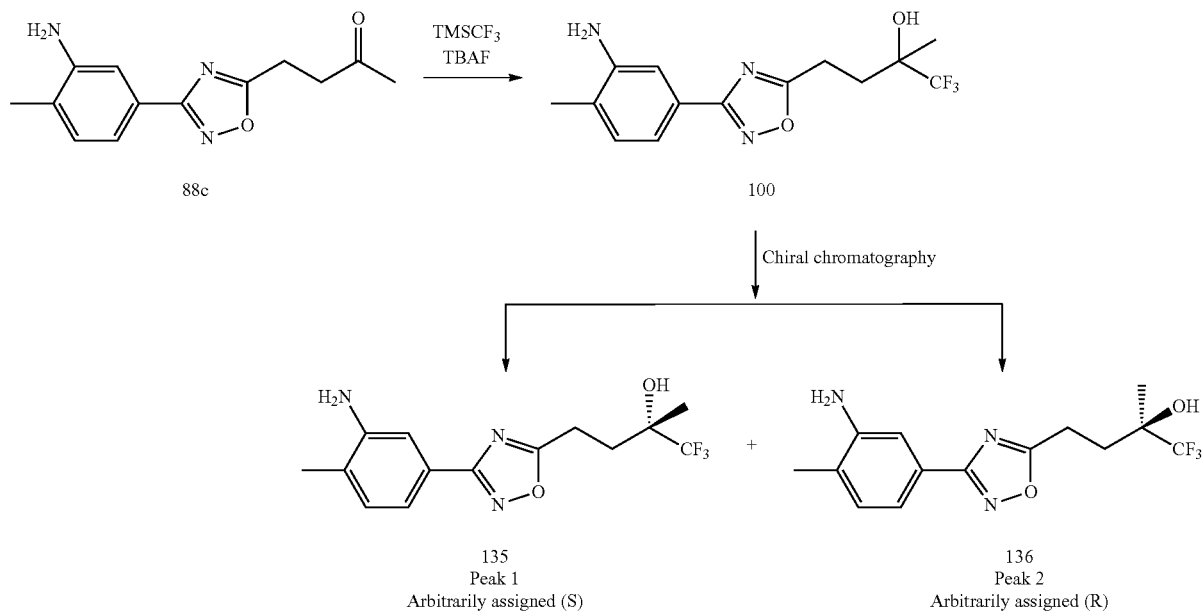
[0507]



[0508] To a solution of ethyl 6-cyanoimidazo[1,2-a]pyridine-3-carboxylate (24q) (265 mg, 1.23 mmol) and 2-methoxyacetohydrazide (193 mg, 1.85 mmol) in 2-ethoxyethanol (5 mL) was added NaOMe (0.5 M in MeOH, 3.7 mL). The mixture was heated at 110° C. in a sealed vial overnight. The reaction mixture was purified by HPLC to give 6-(3-(methoxymethyl)-1H-1,2,4-triazol-5-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (99). MS m/z 274.1 (M+1)<sup>+</sup>.

Synthesis of 4-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)-1,1,1-trifluoro-2-methylbutan-2-ol (100) and SR enantiomers (135 and 136)

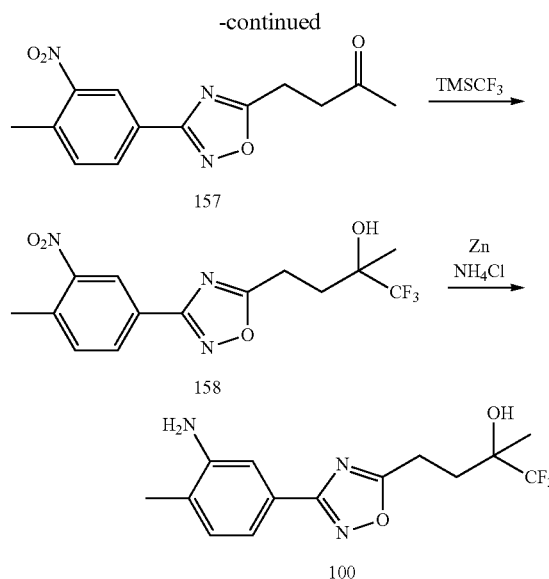
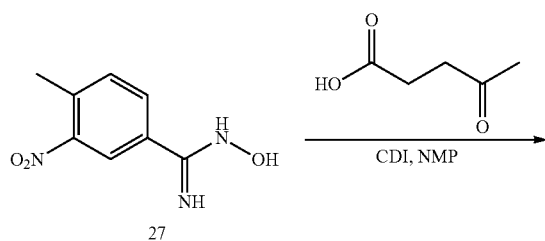
[0509]



[0510] Method A:

[0511] To a solution of 4-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)butan-2-one (88c) (275 mg, 1.12 mmol) and TBAF (0.5 M in THF and 5% water, 2.2 mL) in anhydrous THF (2.5 mL) at 0° C. was added trifluoromethyltrimethylsilane dropwise (excess) and the reaction was stirred to room temperature for 15 minutes. The reaction was checked by LCMS. More trifluoromethyltrimethylsilane was added dropwise until reaction was complete by LCMS. A second batch of TBAF (0.5 M in THF and 5% water, 2.2 mL) was added and the reaction was stirred for 30 minutes. The solvent was concentrated and the crude product was dissolved in ethyl acetate. The organic phase was washed with water then brine and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography to yield 4-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)-1,1,1-trifluoro-2-methylbutan-2-ol (100).  $^1\text{H}$  NMR (400 MHz,  $\text{d}_6$ -DMSO)  $\delta$  7.30 (d,  $J=1.6$  Hz, 1H), 7.09 (m, 2H), 6.09 (s, 1H), 5.18 (s, 2H), 3.10 (m, 2H), 2.02-2.22 (m, 5H), 1.31 (s, 3H). MS  $m/z$  316.1 ( $M+1$ ) $^+$ .

[0512] Method B:



[0513] To a solution of 4-oxopentanoic acid (5.35 g, 46.14 mmol) in NMP (15 mL) was slowly added CDI (7.52 g, 46.14 mmol). The resulting mixture was stirred at room temperature for 30 minutes. Then N-hydroxy-4-methyl-3-nitrobenzimidamide (27) (3.0 g, 15.38 mmol) was added and stirred for another 30 minutes until LCMS indicated complete reaction. The mixture was then heated at 125° C. for 15 minutes in a microwave reactor and poured into water (100 mL). The mixture was extracted with EtOAc (2x50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to give a crude product

which was purified by silica-gel chromatography (0-60% EtOAc in hexanes) to afford 4-(3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl) butan-2-one (157). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.66 (d, J=1.6 Hz, 1H), 8.19 (dd, J=1.6, 8.0 Hz, 1H), 7.48 (d, J=8.0 Hz, 1H), 3.23 (m, 2H), 3.12 (m, 2H), 2.68 (s, 3H), 2.29 (s, 3H). MS m/z 276.1 (M+1)<sup>+</sup>.

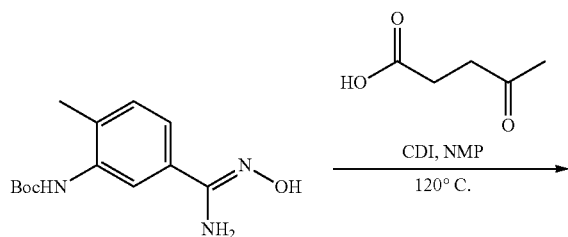
**[0514]** To a solution of 4-(3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl)butan-2-one (157) (2.5 g, 9.08 mmol) and TBAF (0.5 M in THF, 3.6 mL) in anhydrous THF (25 mL) at -25° C. was added trifluoromethyltrimethylsilane dropwise (2.58 g, 18.16 mmol) and the reaction was warmed to room temperature and stirred for 1 hour. The solvent was concentrated and the crude product was dissolved in ethyl acetate. The organic phase was washed with water then brine and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography to yield 1,1,1-trifluoro-2-methyl-4-(3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl) butan-2-ol (158). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.49 (d, J=2.0 Hz, 1H), 8.02 (dd, J=1.6, 8.0 Hz, 1H), 7.31 (d, J=8.0 Hz, 1H), 3.03 (m, 2H), 2.64 (s, 1H), 2.51 (s, 3H), 2.21-2.29 (m, 1H), 2.03-2.11 (m, 1H), 1.30 (s, 3H). MS m/z 346.1 (M+1)<sup>+</sup>.

**[0515]** To a suspension of 1,1,1-trifluoro-2-methyl-4-(3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl)butan-2-ol (158) (2.0 g, 5.79 mmol) in EtOH:H<sub>2</sub>O (4:1) (15 mL) was added zinc dust (1.52 g, 23.2 mmol) and ammonium chloride (1.24 g, 23.2 mmol). The reaction mixture was heated at 85° C. for 8 hours then filtered hot over celite and rinsed with ethyl acetate. The organic phase was washed with saturated aqueous NH<sub>4</sub>Cl (50 mL) then water and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography to yield 4-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)-1,1,1-trifluoro-2-methylbutan-2-ol (100). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 7.30 (d, J=1.6 Hz, 1H), 7.09 (m, 2H), 6.09 (s, 1H), 5.18 (s, 2H), 3.10 (m, 2H), 2.02-2.22 (m, 5H), 1.31 (s, 3H). MS m/z 316.1 (M+1)<sup>+</sup>.

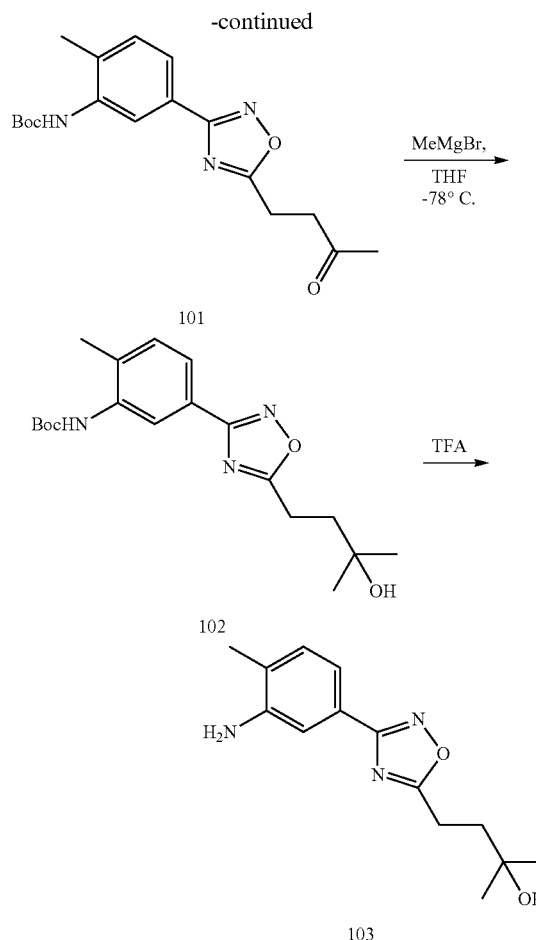
**[0516]** The separation of enantiomers was performed using a 21×250 mm ChiralCel OD-H column at a flow rate of 80 g/min, using CO<sub>2</sub>/Methanol (75:25) at 30° C. Analytical methods using the same column and solvent mixture showed peak 1 eluting at 3.62 min, and peak 2 at 5.35 min. Peak 1 was assigned to be the isomer of (S)-4-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)-1,1,1-trifluoro-2-methylbutan-2-ol (135) which was consistent with F299 and Peak 2 was assigned to be the isomer of (R)-4-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)-1,1,1-trifluoro-2-methylbutan-2-ol (136) which was consistent with F300. MS m/z 316.1 (M+1)<sup>+</sup>.

Synthesis of 4-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)-2-methylbutan-2-ol (103)

**[0517]**



35



**[0518]** CDI (1.06 g, 6.6 mmol) was added in one portion to 4-oxopentanoic acid (0.82 g, 6.6 mmol). After 20 minutes at room temperature *t*-butyl (5-(*N*'-hydroxycarbamimidoyl)-2-methylphenyl)carbamate (35) (2 g, 5.5 mmol) was added. After 1 hour, the solution was heated at 120° C. via microwave for 20 minutes. The solution was partitioned with EtOAc and water and the organic phase was dried over MgSO<sub>4</sub> and evaporated. The residue was purified over silica gel using hexane and EtOAc to give *tert*-butyl (2-methyl-5-(5-(3-oxobutyl)-1,2,4-oxadiazol-3-yl)phenyl)carbamate (101).

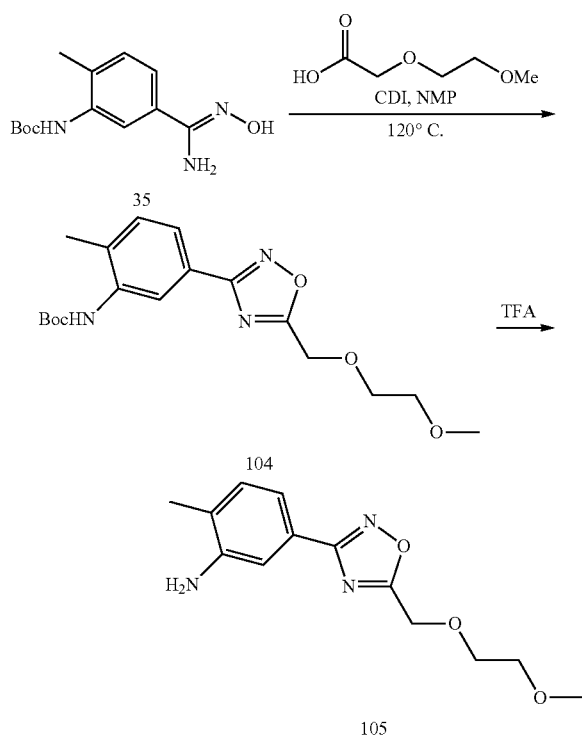
**[0519]** *t*-Butyl (2-methyl-5-(5-(3-oxobutyl)-1,2,4-oxadiazol-3-yl)phenyl)carbamate (101) (2 g, 2.4 mmol) in THF (10 mL) was added to a THF solution of MeMgBr (10 mL, 3 M in Et<sub>2</sub>O) at 78° C. After addition, the solution was warmed to 0° C. and after 30 minutes, quenched with NH<sub>4</sub>Cl. After aqueous work up, the residue was purified by silica gel to give *tert*-butyl (5-(5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)carbamate (102) as a solid. MS m/z 362.2 (M+1)<sup>+</sup>.

**[0520]** TFA (20 mL) was added to (5-(5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)carbamate (102) and stirred for 30 minutes. The volatiles were then evaporated and the residue was partitioned in dichloromethane and saturated NaHCO<sub>3</sub>. The organic phase was then isolated and solvent evaporated. The residue was purified over silica gel using EtOAc in hexanes to give 4-(3-(3-

amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)-2-methylbutan-2-ol (103) as an oil which solidified upon standing. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.40-7.36 (m, 2H), 7.14 (d, J=8 Hz, 1H), 3.07 (dd, J=8.4, 7.6 Hz, 2H), 2.21 (s, 3H), 2.06 (dd, J=8.4, 7.6 Hz, 2H), 1.31 (s, 6H). MS m/z 262.2 (M+1)<sup>+</sup>.

Synthesis of 5-(5-((2-methoxyethoxy)methyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (105)

[0521]

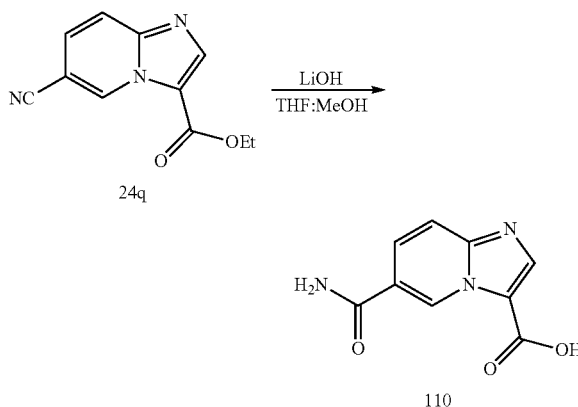


[0522] CDI (2.44 g, 15.11 mmol) was added portionwise to a stirred solution of 2-(2-methoxyethoxy)acetic acid (2.02 g, 15.11 mmol) in dry NMP (10 mL). After 20 minutes, t-butyl (5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)carbamate (35) (3.34 g, 12.59 mmol) was added to the solution and stirred for 1 hour. After which, the solution was heated at 120°C via microwave for 20 minutes. The solution was partitioned with EtOAc and water and the organic phase was dried over MgSO<sub>4</sub> and evaporated. The residue was purified over silica gel using hexane and EtOAc to give t-butyl (5-(5-((2-methoxyethoxy)methyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)carbamate (104).

[0523] TFA (20 mL) was added to t-butyl (5-(5-((2-methoxyethoxy)methyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)carbamate (104) and stirred for 2 hours. The volatiles were then evaporated and the residue was partitioned in dichloromethane and saturated NaHCO<sub>3</sub>. The organic phase was then isolated and solvent evaporated. The residue was purified over silica gel using EtOAc in hexanes to give 5-(5-((2-methoxyethoxy)methyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (105) as an oil which solidified on standing. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.44-7.40 (m, 2H), 7.15 (d, J=8.0 Hz, 1H), 4.86 (s, 2H), 3.84-3.82 (m, 2H), 3.64-3.61 (m, 2H), 3.39 (s, 3H), 2.22 (s, 3H). MS m/z 264.1 (M+1)<sup>+</sup>.

Synthesis of 6-carbamoylimidazo[1,2-a]pyridine-3-carboxylic acid (110)

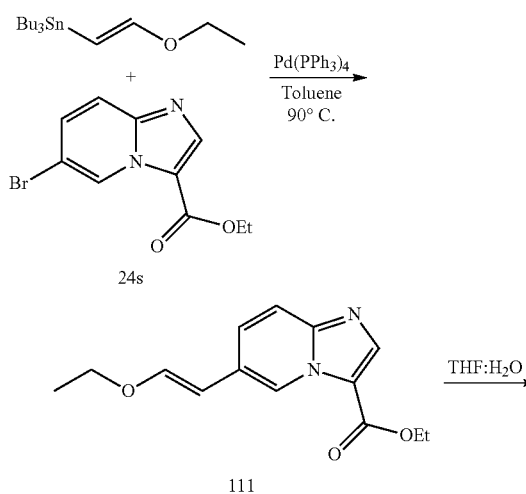
[0524]

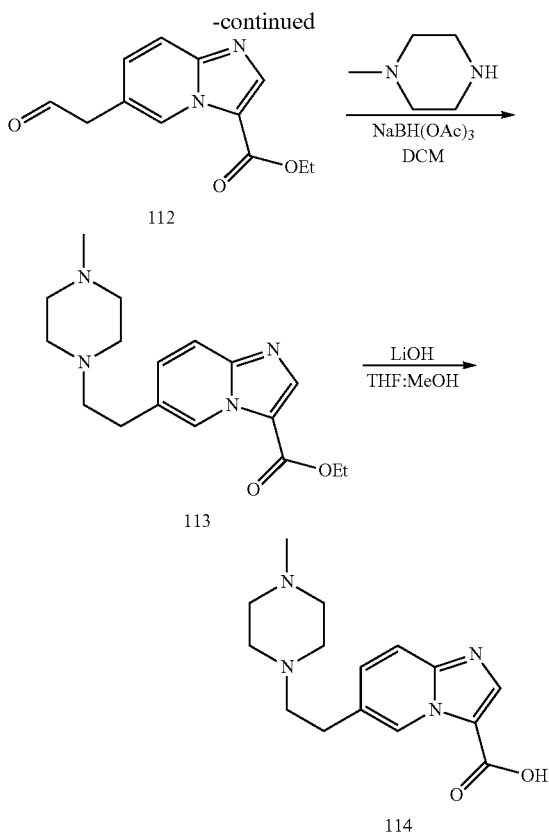


[0525] To a stirring solution of ethyl 6-cyanoimidazo[1,2-a]pyridine-3-carboxylate (24q) (500 mg, 2.32 mmol) in THF:MeOH (4:1, 5 mL) was added 2N LiOH (4 mL). The reaction was heated at 60°C for 2 h then acidified with 10% citric acid. The solvent was partially concentrated and the resulting solid was collected by vacuum filtration and was washed with excess water. The product was purified from the crude solid to afford 6-carbamoylimidazo[1,2-a]pyridine-3-carboxylic acid (110). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 9.80 (s, 1H), 8.33-8.31 (m, 1H), 8.29 (s, 1H), 7.95 (dd, J=2.0, 9.6 Hz, 1H), 7.83 (dd, J=0.8, 9.2 Hz, 1H), 7.69 (s, 1H). MS m/z 205.05 (M+1)<sup>+</sup>.

Synthesis of 6-(2-(4-methylpiperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (114)

[0526]





**[0527]** To a stirring mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (24s) (1 g, 3.72 mmol) and tetrakis (triphenylphosphine)palladium(0) (215 mg, 0.19 mmol) in anhydrous toluene (10 mL) under argon was added tributyl [2-ethoxyethenyl]stannane (1.7 g, 4.65 mmol). The reaction mixture was heated in a microwave sealed tube overnight at 90° C. The reaction was cooled to room temperature and was filtered through celite. The solvent was concentrated and the crude product was purified by silica chromatography to afford (E)-ethyl 6-(2-ethoxyvinyl)imidazo[1,2-a]pyridine-3-carboxylate (111). MS *m/z* 261.3 (M+1)<sup>+</sup>.

**[0528]** A stirring solution of ethyl 6-(2-ethoxyvinyl)imidazo[1,2-a]pyridine-3-carboxylate (111) (240 mg, 1.15 mmol) in THF:H<sub>2</sub>O (1:1, 4 mL) was heated at 50° C. overnight. The reaction was cooled to room temperature and neutralized with saturated solution of sodium bicarbonate. The crude product was extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was concentrated and crude ethyl 6-(2-oxoethyl)imidazo[1,2-a]pyridine-3-carboxylate (112) was used in the next step without further purification. MS *m/z* 233.3 (M+1)<sup>+</sup>.

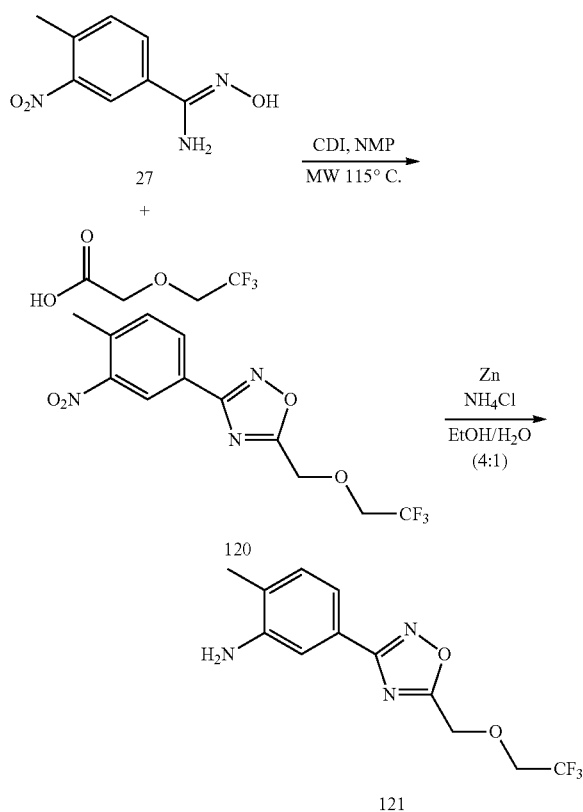
**[0529]** To a stirring solution of crude ethyl 6-(2-oxoethyl)imidazo[1,2-a]pyridine-3-carboxylate (112) (214 mg, 0.92 mmol) in DCM (5 mL) and 1-methylpiperazine (231  $\mu$ L, 2.30 mmol) at room temperature was added portion-wise sodium triacetoxyborohydride (586 mg, 2.77 mmol). The reaction was stirred at room temperature overnight. The solvent was concentrated. The crude was taken in 10% sodium bicarbonate and ethyl acetate. The organic was washed with water, brine and dried over anhydrous sodium sulfate. The solvent

was concentrated and the crude product was purified by silica chromatography to afford methyl 6-(2-(4-methylpiperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-3-carboxylate (113). MS *m/z* 304.4 (M+1)<sup>+</sup>.

**[0530]** To a stirring solution of methyl 6-(2-(4-methylpiperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-3-carboxylate (113) (215 mg, 0.68 mmol) in THF:MeOH (4:1, 4 mL) was added 2N LiOH (3 mL). The reaction was heated at 60° C. for 45 minutes. The pH was adjusted between 4-5 with 1N HCl and concentrated. The crude product was purified by preparative HPLC to afford 6-(2-(4-methylpiperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (114). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO)  $\delta$  9.25 (s, 1H), 8.35 (s, 1H), 7.83 (d, J=9.2 Hz, 1H), 7.61 (dd, J=1.6, 9.2 Hz, 1H), 4.65-4.19 (m, 8H), 3.49-3.30 (m, 2H), 3.04-2.99 (m, 2H), 2.81 (s, 3H). MS *m/z* 316.1 (M+1)<sup>+</sup>.

Synthesis of 2-methyl-5-(5((2,2,2-trifluoroethoxy)methyl)-1,2,4-oxadiazol-3-yl)aniline (121)

**[0531]**



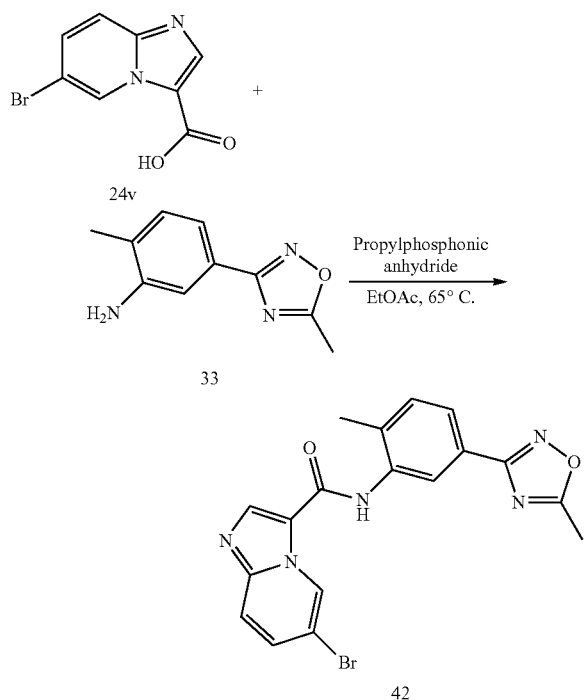
**[0532]** To a stirring solution of 2-(2,2,2-trifluoroethoxy)acetic acid (1.06 g, 6.33 mmol) in anhydrous NMP (12 mL) was added 1,1'-carbonyldiimidazole (CDI) (1.01 g, 6.33 mmol). The reaction was stirred for 5 minutes. N'-hydroxy-4-methyl-3-nitrobenzimidamide (27) (1.24 g, 6.33 mmol) was added and the reaction was stirred for 25 minutes then heated in the microwave at 115° C. for 12 minutes. The crude product was extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was concentrated and the crude

product was purified by silica chromatography to yield 3-(4-methyl-3-nitrophenyl)-5-((2,2,2-trifluoroethoxy)methyl)-1,2,4-oxadiazole (120). MS  $m/z$  318.1 (M+1)<sup>+</sup>.

**[0533]** To a suspension of 3-(4-methyl-3-nitrophenyl)-5-((2,2,2-trifluoroethoxy)methyl)-1,2,4-oxadiazole (120) (1.28 g, 4.03 mmol) in EtOH:H<sub>2</sub>O (4:1) (21 mL) was added zinc dust (1.05 g, 16.1 mmol) and ammonium chloride (862 mg, 16.1 mmol). The reaction mixture was heated at 85° C. for 3 hours then filtered hot over celite and rinsed with ethyl acetate. The solvent was concentrated to give 2-methyl-5-((2,2,2-trifluoroethoxy)methyl)-1,2,4-oxadiazol-3-yl)aniline (121). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 7.32 (s, 1H), 7.14-7.08 (m, 2H), 5.21 (s, 2H), 5.08 (s, 2H), 4.34 (q, J=9.2 Hz, 2H), 2.11 (s, 3H). MS  $m/z$  288.1 (M+1)<sup>+</sup>.

Synthesis of 6-bromo-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (42)

**[0534]**

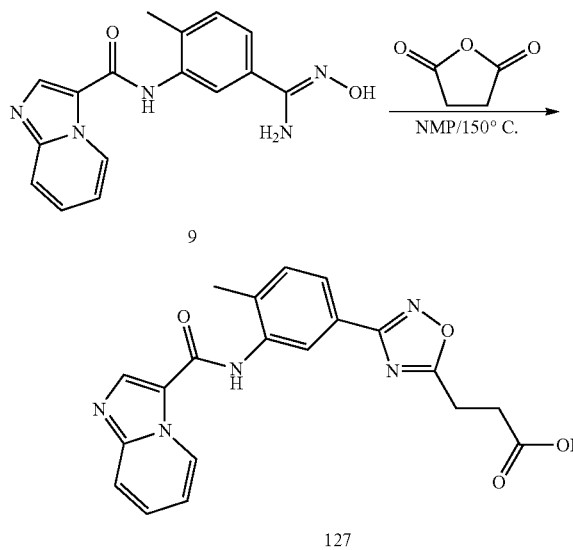


**[0535]** To a stirring suspension of 6-bromoimidazo[1,2-a]pyridine-3-carboxylic acid (637 mg, 2.64 mmol) and 2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)aniline (33) (500 mg, 2.64 mmol) in ethyl acetate (8 mL) was added propylphosphonic anhydride solution 50 wt. in ethyl acetate (3.1 mL, 5.29 mmol). The reaction was heated at 65° C. overnight. The reaction was cooled to room temperature and diluted with a solution of saturated sodium bicarbonate. The organic was separated and washed with 2× water/brine mixture and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography, DCM:EtOAc:MeOH (1:1:0.1) to yield 6-bromo-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (42). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.13 (s, 1H), 9.63-9.62 (m, 1H), 8.60 (s, 1H), 8.07 (d, J=2.0 Hz, 1H), 7.83-7.79 (m, 2H),

7.68 (dd, J=2.0, 9.6 Hz, 1H), 7.50 (d, J=8.0 Hz, 1H), 2.67 (s, 3H), 2.37 (s, 3H). MS  $m/z$  412, 414 (M+1)<sup>+</sup>.

Synthesis of 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)propanoic acid (127)

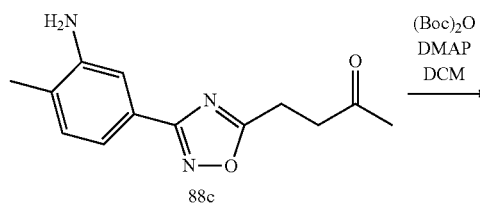
**[0536]**



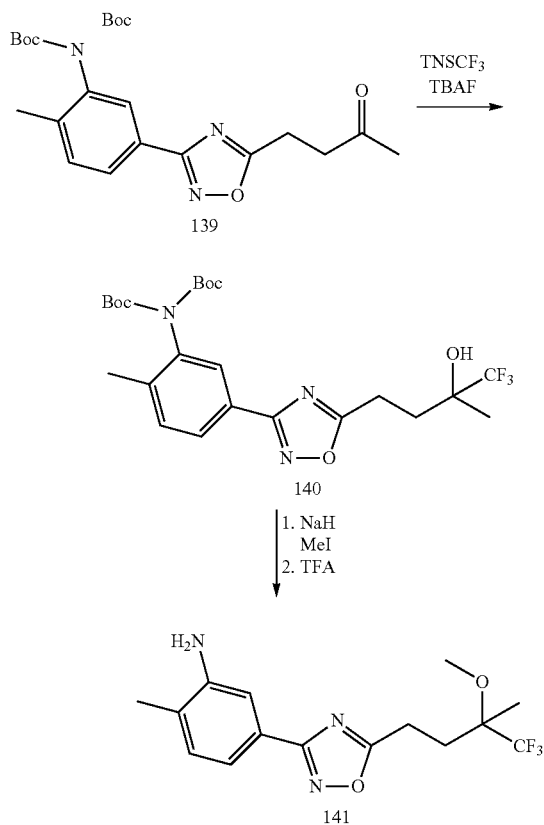
**[0537]** A mixture of N-(5-(N<sup>h</sup>-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9) (50 mg, 0.162 mmol) and succinic anhydride (49 mg, 0.485 mmol) in anhydrous NMP (1 mL) was heated at 150° C. for 20 minutes. The cooled reaction was poured into a flask containing ice water. The resulting solid 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)propanoic acid (127) was collected by vacuum filtration. <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.12 (s, 1H), 9.50-9.48 (m, 1H), 8.65 (s, 1H), 8.05 (d, J=1.6 Hz, 1H), 7.85-7.80 (m, 2H), 7.64-7.60 (m, 1H), 7.50 (d, J=8.4 Hz, 1H), 7.27-7.24 (m, 1H), 3.19 (t, J=7.2 Hz, 2H), 2.84 (t, J=7.2 Hz, 2H), 2.36 (s, 3H). MS  $m/z$  392.13 (M+1)<sup>+</sup>.

Synthesis of 2-methyl-5-(5-(4,4,4-trifluoro-3-methoxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)aniline (141)

**[0538]**



-continued



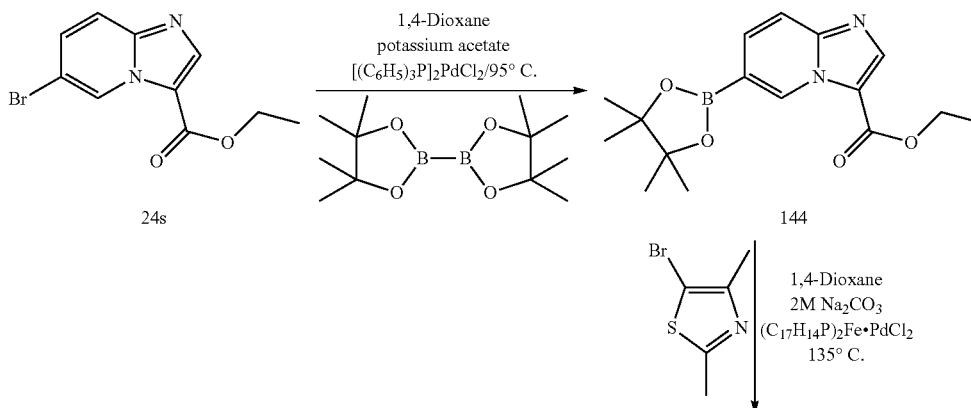
**[0539]** (Boc)<sub>2</sub>O (535 mg, 2.45 mmol) was added to a stirred solution of 4-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)butan-2-one (88c) (200 mg, 0.82 mmol) and DMAP (catalytic amount) in dichloromethane (2 mL). The reaction was stirred at room temperature overnight. The mixture was diluted with dichloromethane (20 mL) and washed with brine. The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>,

filtered and concentrated to give 4-(3-(3-[bis[(1,1-dimethylethoxy)carbonyl]amino]-4-methylphenyl)-1,2,4-oxadiazol-5-yl)butan-2-one (139) (200 mg, 55% yield). MS *m/z* 468.1 (M+23)<sup>+</sup>.

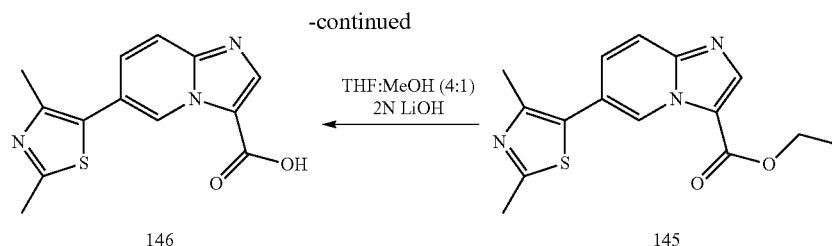
**[0540]** To a solution of 4-(3-(3-[bis[(1,1-dimethylethoxy)carbonyl]amino]-4-methylphenyl)-1,2,4-oxadiazol-5-yl)butan-2-one (139) (200 mg, 0.45 mmol) and TBAF (0.5 M in THF, 0.9 mL) in anhydrous THF (2.5 mL) at 0° C. was added trifluoromethyltrimethylsilane dropwise (excess) and the reaction was stirred to room temperature for 15 minutes. The reaction was checked by LCMS. More trifluoromethyltrimethylsilane was added dropwise until reaction was completed by LCMS. The reaction was quenched with water, then the solvent was removed and the crude product was dissolved in ethyl acetate. The organic phase was washed with water then brine and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography to yield 4-(3-(3-[bis[(1,1-dimethylethoxy)carbonyl]amino]-4-methylphenyl)-1,2,4-oxadiazol-5-yl)-1,1,1-trifluoro-2-methylbutan-2-ol (140) <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.89 (d, J=8.0 Hz, 1H), 7.77 (s, 1H), 7.32 (d, J=8.0 Hz, 1H), 3.16 (m, 2H), 2.16-2.44 (m, 5H), 1.39 (m, 18H), 1.24 (s, 3H). MS *m/z* 538.1 (M+23)<sup>+</sup>.

**[0541]** To a solution of 4-(3-(3-[bis[(1,1-dimethylethoxy)carbonyl]amino]-4-methylphenyl)-1,2,4-oxadiazol-5-yl)-1,1,1-trifluoro-2-methylbutan-2-ol (140) (27 mg, 0.052 mmol) in NMP (1.0 mL) was added NaH (12.5 mg, 60% wt in mineral oil, 0.312 mmol) and MeI (44 mg, 0.312 mmol). The resulting mixture was heated at 90° C. for 1 hour. The reaction was quenched with water and extracted with EtOAc. The organic layers were combined and concentrated to yield a residue which was dissolved in TFA (0.5 mL) and stirred at room temperature for 10 minutes. Then 2M aqueous Na<sub>2</sub>CO<sub>3</sub> (5 mL) was added and extracted with EtOAc. The organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give crude 2-methyl-5-(5-(4,4,4-trifluoro-3-methoxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)aniline (141) which was used without further purification. MS *m/z* 344.1 (M+1)<sup>+</sup>.

Synthesis of 6-(2,4-dimethylthiazol-5-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (146)

**[0542]**





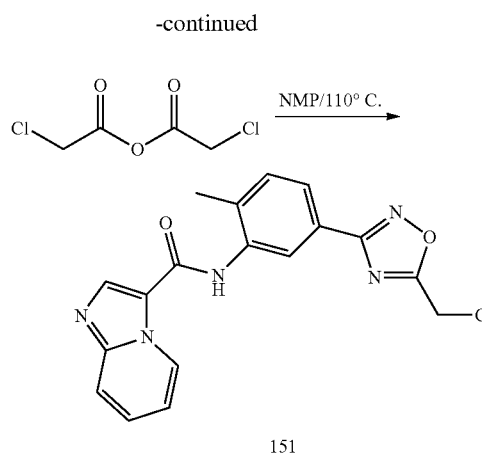
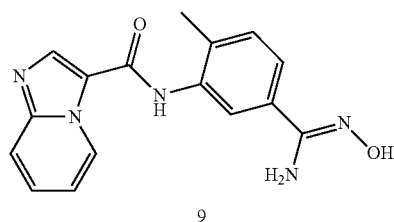
**[0543]** A mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (24s) (500 mg, 1.86 mmol), bis(pinacolato)diboron (472 mg, 1.86 mmol), dichloro-bis(triphenylphosphine)palladium (65 mg, 0.093 mmol) and potassium acetate (456 mg, 4.65 mmol) in anhydrous dioxane (8 mL) was heated at 95° C. for 4 hours. The reaction turned black. The reaction was cooled and filtered through celite. The solvent was concentrated. The oil was taken in EtOAc. The organic was washed with water/brine mixture, brine and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography. MS *m/z* 317 (M+1)<sup>+</sup>.

**[0544]** A mixture of 5-bromo-2,4-dimethylthiazole (171 mg, 0.89 mmol), ethyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-a]pyridine-3-carboxylate (144) (250 mg, 1.07 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (39 mg, 0.05 mmol) and a solution of 2M sodium carbonate (300  $\mu$ L) in anhydrous dioxane (4 mL) was heated in the microwave at 135° C. for 25 minutes. The reaction was filtered through celite. The crude product was taken in water and ethylacetate. The organic was washed with water/brine mixture and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography. MS *m/z* 302.09 (M+1)<sup>+</sup>.

**[0545]** A mixture of ethyl 6-(2,4-dimethylthiazol-5-yl)imidazo[1,2-a]pyridine-3-carboxylate (145) (190 mg, 0.630 mmol) and 2N LiOH (1 mL) in THF:MeOH (4:1, 4 mL) was heated at 60° C. for 30 minutes. The reaction was cooled to room temperature and the pH was adjusted between 4-5 with 10% citric acid. The solvent was partially reduced and the resulting solid was collected by vacuum filtration to give 6-(2,4-dimethylthiazol-5-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (146). <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO)  $\delta$  9.34 (s, 1H), 8.29 (s, 1H), 7.87 (dd, *J*=0.8, 9.2 Hz, 1H), 7.62 (dd, *J*=2.0, 9.2 Hz, 1H), 2.66 (s, 3H), 2.41 (s, 3H). MS *m/z* 274.06 (M+1)<sup>+</sup>.

Synthesis of N-(5-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (151)

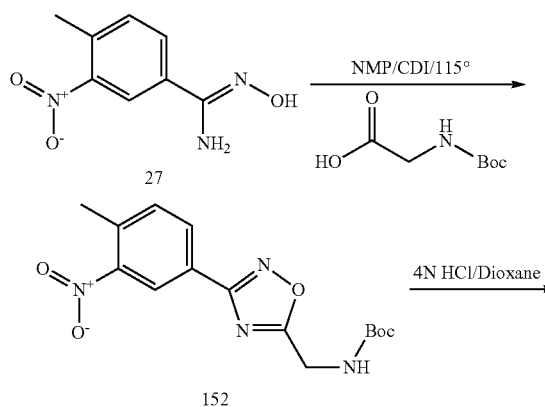
**[0546]**

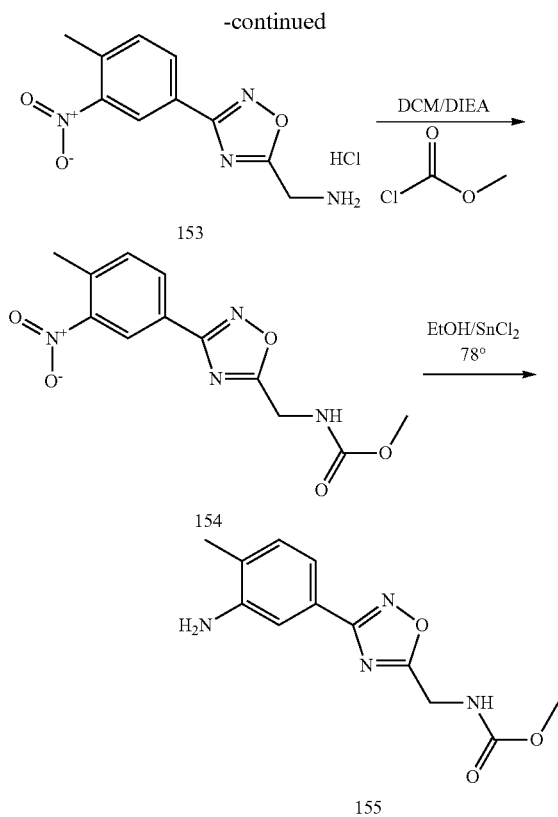


**[0547]** A mixture of N-(5-(N<sup>1</sup>-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9) (500 mg, 1.62 mmol) and 2-chloroacetic anhydride (553 mg, 3.23 mmol) in anhydrous 1-methyl-2-pyrrolidinone (10 mL) was heated in the microwave at 110° C. for 12 minutes. The crude was diluted with water and extracted with ethyl acetate. The organic was washed with water/brine mixture and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography. MS *m/z* 368.08 (M+1)<sup>+</sup>.

Synthesis of (3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methylcarbamate (155)

**[0548]**





**[0549]** To a stirring solution of Boc-GLY-OH (2.7 g, 15.37 mmol) in anhydrous 1-methyl-2-pyrrolidinone (12 mL) was added 1,1'-carbonyldiimidazole (2.5 g, 15.37 mmol). The reaction was stirred for 5 minutes. Then, N'-hydroxy-4-methyl-3-nitrobenzimidamide (27) (2 g, 10.25 mmol) was added and the reaction was stirred for 25 minutes. Next, the reaction was heated in the microwave at 115° C. for 12 minutes. The crude product was extracted with ethyl acetate. The organic was washed with water/brine mixture, brine and dried over anhydrous sodium sulfate. The solvent was concentrated and the crude product was taken in DCM and minimal THF and purified by silica chromatography.

**[0550]** To stirring suspension of tert-butyl ((3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl)methyl)carbamate (152) (2.9 g, 8.67 mmol) in acetonitrile (5 mL) was added 4N HCl in dioxane (12 mL). The reaction was stirred at room temperature for 1.5 hours. The solvent was concentrated and the crude product was dried under high vacuum.

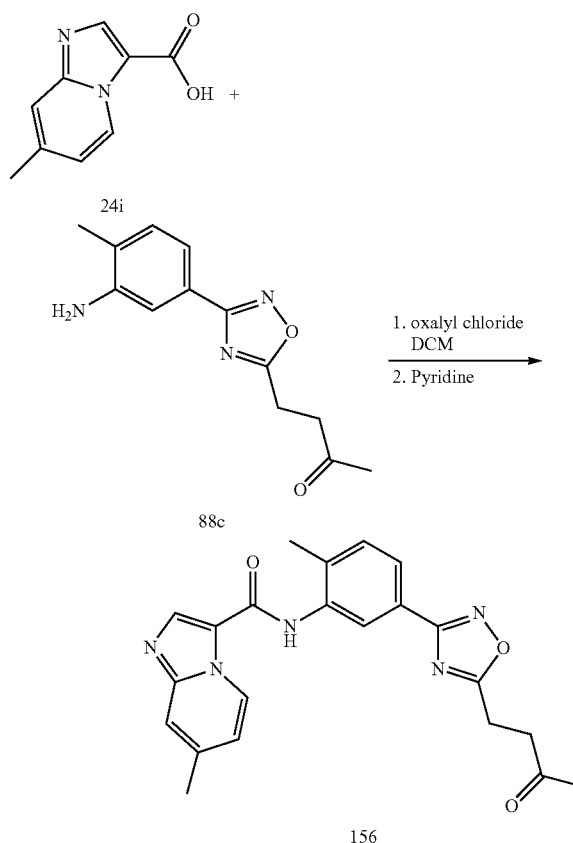
**[0551]** To a stirring solution of (3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl)methanamine hydrochloride (153) (825 mg, 2.78 mmol) N,N-diisopropylethylamine (3.8 mL, 21.69 mmol) in anhydrous dichloromethane (35 mL) at 0° C. was added drop-wise of methyl chloroformate (670  $\mu$ L, 8.67 mmol). The reaction was stirred to room temperature for 25 minutes. The crude was purified by silica chromatography.

**[0552]** To a stirring suspension of methyl ((3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl)methyl)carbamate (1 g, 3.42 mmol) in ethanol (20 mL) was added stannous chloride dihydrate (3.1 g, 13.69 mmol). The reaction mixture was heated at 78° C. for 3 hours. The reaction was cooled to room temperature and the solvent was partially reduced. The pH was adjusted to slightly basic with a saturated solution of

sodium bicarbonate. The resulting white suspension was filtered and washed with water and ethyl acetate. The aqueous was extracted with ethyl acetate and washed with water, brine and dried over anhydrous sodium sulfate. The solvent was concentrated to afford the product. The crude product was used in the next step without further purification. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO)  $\delta$  8.03 (t, *J*=6.0 Hz, 1H), 7.28 (d, *J*=1.2 Hz, 1H), 7.10-7.06 (m, 2H), 5.19 (s, 2H), 4.52 (d, *J*=6.0 Hz, 2H), 3.59 (s, 3H), 2.10 (s, 3H). MS *m/z* 263.11 (M+1)<sup>+</sup>.

Synthesis of 7-methyl-N-(2-methyl-5-(5-(3-oxobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (156)

**[0553]**

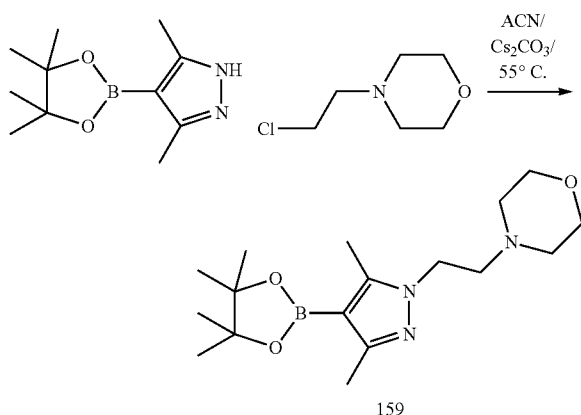


**[0554]** To a stirring suspension of 7-methylimidazo[1,2-a]pyridine-3-carboxylic acid (24i) (975 mg, 5.54 mmol) in anhydrous dichloromethane (5 mL) was added dropwise oxalyl chloride (1.45 mL, 16.62 mmol). Then, a drop of anhydrous DMF was added and the reaction mixture was stirred at room temperature for 30 minutes. The solvent was concentrated and the crude solid was added to a stirring solution of 4-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)butan-2-one (88c) (1.26 g, 5.14 mmol) in anhydrous pyridine (5 mL) at room temperature. The reaction was stirred at room temperature for 20 minutes. Then water (100 mL) was added and stirred for 10 minutes. The precipitate was filtered and dried in air to give a solid of 7-methyl-N-(2-methyl-5-(5-(3-oxobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (156). <sup>1</sup>H NMR (400

MHz,  $d_6$ -DMSO)  $\delta$  9.97 (s, 1H), 9.33 (d,  $J=7.2$  Hz, 1H), 8.52 (s, 1H), 8.04 (d,  $J=2.0$  Hz, 1H), 7.78 (dd,  $J=1.6, 8.0$  Hz, 1H), 7.58 (m, 1H), 7.48 (d,  $J=8.4$  Hz, 1H), 7.03 (dd,  $J=1.6, 7.2$  Hz, 1H), 3.11 (m, 4H), 2.43 (s, 3H), 2.36 (s, 3H), 2.18 (s, 3H). MS  $m/z$  404.1 (M+1)<sup>+</sup>.

Synthesis of 4-(2-(3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)ethyl)morpholine (159)

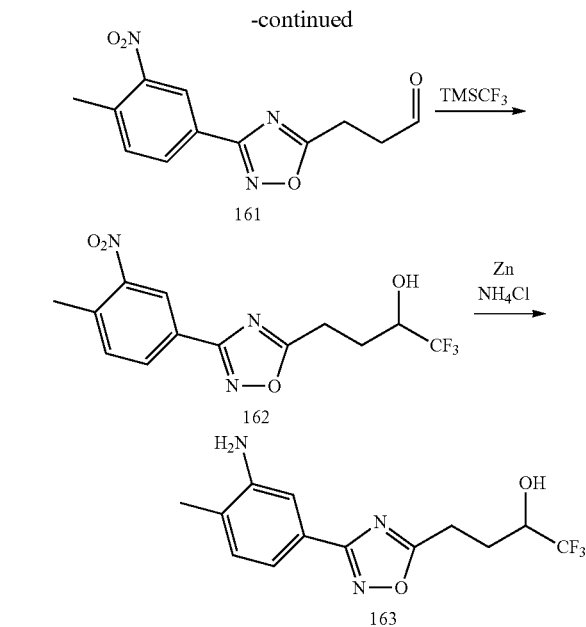
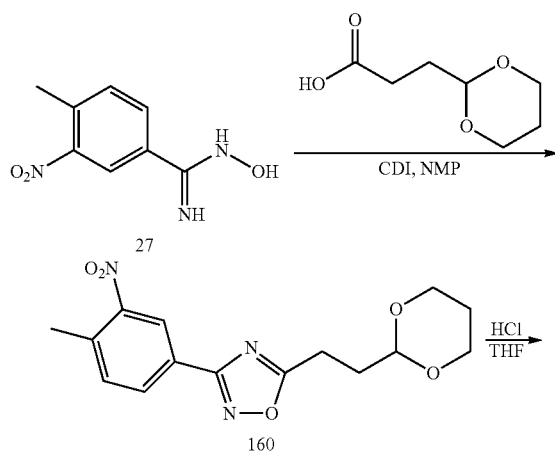
[0555]



[0556] A mixture of 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (500 mg, 2.25 mmol), 4-(2-chloroethyl)morpholine (404 mg, 2.70 mmol) and cesium carbonate (1.5 g, 2.7 mmol) in anhydrous acetonitrile (10 mL) was heated at 55° C. overnight. The reaction was cooled to room temperature and filtered. The solvent was concentrated and the crude product was dried under vacuo. The crude product was used in the next step without further purification. MS  $m/z$  334.2 (M+1)<sup>+</sup>.

Synthesis of 4-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)-1,1,1-trifluorobutan-2-ol (163)

[0557]



[0558] To a solution of 3-(1,3-dioxan-2-yl)propanoic acid (1.2 g, 7.5 mmol) in NMP (15 mL) was slowly added CDI (1.22 g, 7.5 mmol). The resulting mixture was stirred at room temperature for 30 minutes. Then N-hydroxy-4-methyl-3-nitrobenzimidamide (27) (1.46 g, 7.5 mmol) was added and stirred for another 30 minutes. The mixture was then heated at 125° C. for 15 minutes in a microwave reactor and poured into water (100 mL). The mixture was extracted with EtOAc (2x50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude product which was purified by silica-gel chromatography (0-40% EtOAc in hexanes) to afford 5-(2-(1,3-dioxan-2-yl)ethyl)-3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazole (160). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.68 (d,  $J=1.7$  Hz, 1H), 8.20 (dd,  $J=1.7, 8.0$  Hz, 1H), 7.48 (d,  $J=8.0$  Hz, 1H), 4.71 (t,  $J=4.7$  Hz, 1H), 4.15-4.05 (m, 2H), 3.85-3.67 (m, 2H), 3.11 (t,  $J=7.6$  Hz, 2H), 2.68 (s, 3H), 2.19 (m, 2H), 2.16-2.06 (m, 1H), 1.4-1.34 (m, 1H). MS  $m/z$  320.1 (M+1)<sup>+</sup>.

[0559] A solution of 5-(2-(1,3-dioxan-2-yl)ethyl)-3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazole (160) (1.8 g, 5.6 mmol) in 6N HCl (20 mL) and THF (20 mL) was heated at 80° C. for overnight. Then the reaction mixture was neutralized by addition of saturated aqueous Na<sub>2</sub>CO<sub>3</sub>, extracted with EtOAc, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give a crude product which was purified by silica-gel chromatography (0-40% EtOAc in hexanes) to afford 3-(3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl)propanal (161). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.93 (s, 1H), 8.67 (d,  $J=1.7$  Hz, 1H), 8.19 (dd,  $J=1.8, 8.0$  Hz, 1H), 7.49 (d,  $J=8.0$  Hz, 1H), 3.72 (t,  $J=6.3$  Hz, 2H), 3.61 (t,  $J=6.6$  Hz, 2H), 2.69 (s, 3H). MS  $m/z$  262.1 (M+1)<sup>+</sup>.

[0560] To a solution of 3-(3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl)propanal (161) (0.82 g, 3.14 mmol) and TBAF (1.0 M in THF, 0.62 mL) in anhydrous THF (25 mL) at -25° C. was added trifluoromethyltrimethylsilane dropwise (1.8 g, 12.56 mmol) and the reaction was warmed to room temperature and stirred for 1 hour. The solvent was concentrated and the crude product was dissolved in ethyl acetate. The organic phase was washed with water then brine and dried over anhydrous sodium sulfate. The crude product was

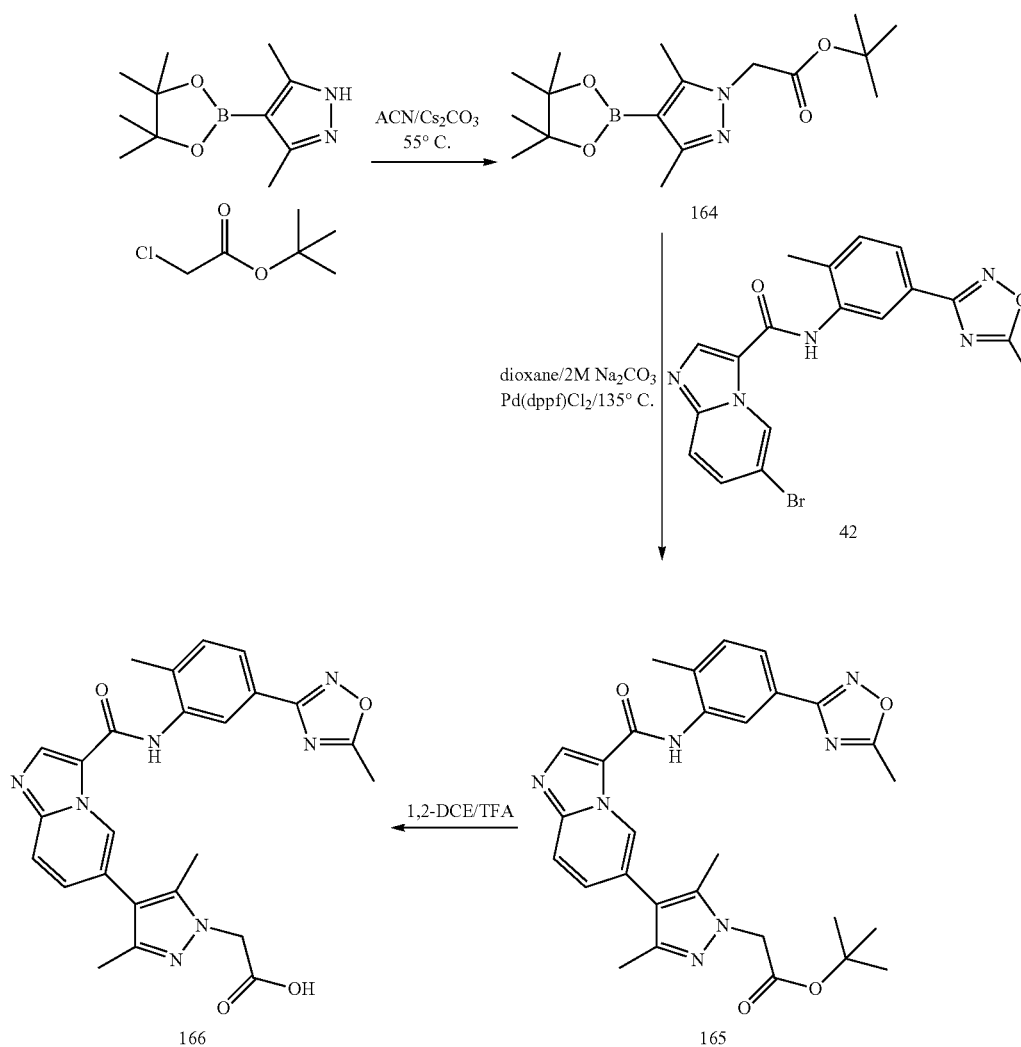
purified by silica chromatography to yield 1,1,1-trifluoro-4-(3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl)butan-2-ol (162).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.50 (d,  $J=1.7$  Hz, 1H), 8.02 (dd,  $J=1.8, 8.0$  Hz, 1H), 7.33 (d,  $J=8.0$  Hz, 1H), 4.03 (m, 1H), 3.49 (dt,  $J=6.4, 44.5$  Hz, 1H), 3.07 (t,  $J=7.2$  Hz, 2H), 2.52 (s, 3H), 2.19 (m, 1H), 2.13-1.98 (m, 1H). MS  $m/z$  332.0 ( $\text{M}+1$ ) $^+$ .

**[0561]** To a suspension of 1,1,1-trifluoro-4-(3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl)butan-2-ol (162) (0.12 g, 0.36 mmol) in  $\text{EtOH}:\text{H}_2\text{O}$  (4:1) (5 mL) was added zinc dust (92 mg, 1.44 mmol) and ammonium chloride (77 mg, 1.44 mmol). The reaction mixture was heated at  $85^\circ\text{C}$ . for overnight, then filtered hot over celite and rinsed with ethyl acetate. The organic phase was washed with saturated aque-

ous  $\text{NH}_4\text{Cl}$  (50 mL) then water and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography to yield 4-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)-1,1,1-trifluorobutan-2-ol (163).  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  7.44 (d,  $J=1.2$  Hz, 1H), 7.26 (d,  $J=7.7$  Hz, 1H), 7.16 (d,  $J=7.8$  Hz, 1H), 6.42 (s, 2H), 4.13 (m, 1H), 3.19-3.05 (m, 2H), 2.16 (s, 3H), 2.14-2.08 (m, 1H), 2.08-1.86 (m, 1H). MS  $m/z$  302.1 ( $\text{M}+1$ ) $^+$ .

Synthesis of 2-(3,5-dimethyl-4-(34(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)-1H-pyrazol-1-yl)acetic acid (166)

**[0562]**



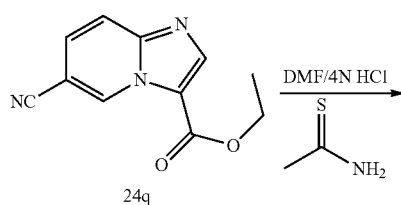
**[0563]** A mixture of 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (500 mg, 2.25 mmol), tert-butyl chloroacetate (538 mg, 2.70 mmol) and cesium carbonate (1.5 g, 2.70 mmol) in anhydrous acetonitrile (10 mL) was heated at 55° C. for 6 h. The reaction was cooled to room temperature and filtered. The solvent was concentrated and the crude product was dried under vacuo. The crude product (164) was used in the next step without further purification. MS  $m/z$  336.22 (M+1)<sup>+</sup>.

**[0564]** A mixture of 6-bromo-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (42) (100 mg, 0.243 mmol), tert-butyl 2-(3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)acetate (164) (90 mg, 0.267 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (18 mg, 0.024 mmol) and a solution of 2M sodium carbonate (300  $\mu$ L) in anhydrous dioxane (1.5 mL) was heated in the microwave at 135° C. for 20 minutes. The reaction was repeated 4 times and all reactions combined. The solvent was reduced under vacuo. The crude product was taken in ethylacetate and water. The organic was washed with 2 $\times$  water/brine and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography to obtain a tan solid (165) (295 mg, 56%). <sup>1</sup>H NMR (400 MHz,  $d_6$ -DMSO)  $\delta$  10.06 (s, 1H), 9.35 (s, 1H), 8.61 (s, 1H), 8.04 (d, J=1.6 Hz, 1H), 7.84 (dd, J=0.8, 9.2 Hz, 1H), 7.80 (dd, J=1.6, 7.6 Hz, 1H), 7.51-7.48 (m, 2H), 4.90 (s, 2H), 2.66 (s, 3H), 2.35 (s, 3H), 2.20 (s, 3H), 2.17 (s, 3H), 1.44 (s, 9H). MS  $m/z$  541.24 (M+1)<sup>+</sup>.

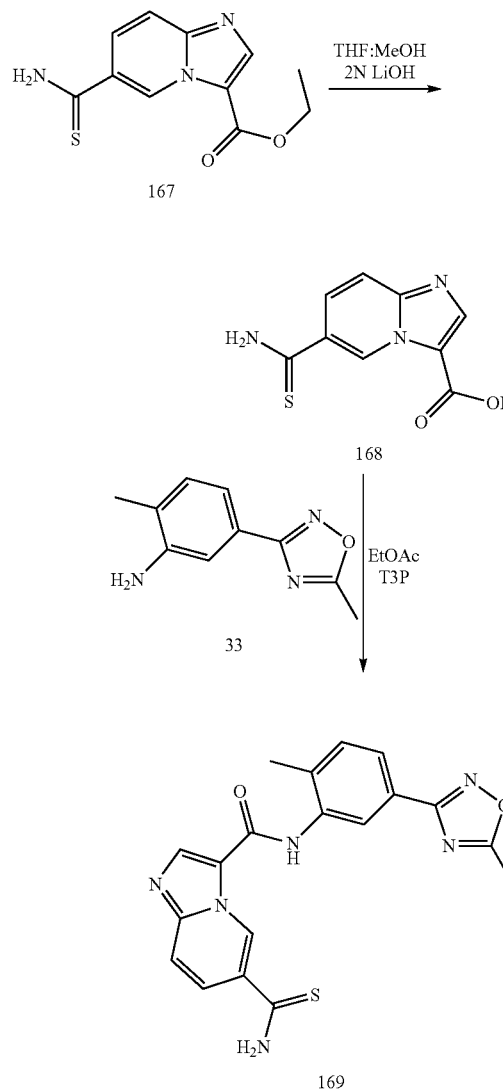
**[0565]** To a stirring solution of tert-butyl 2-(3,5-dimethyl-4-(3-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl-carbamoyl)imidazo[1,2-a]pyridin-6-yl)-1H-pyrazol-1-yl)acetate (165) (286 mg, 0.528 mmol) in 1,2-dichloroethane (2 mL) was added trifluoroacetic acid (1 mL). The reaction was heated at 50° C. for 3 h. Then, the reaction was cooled to room temperature and the solvent was concentrated. The crude product (166) was used without further purification. <sup>1</sup>H NMR (400 MHz,  $d_6$ -DMSO)  $\delta$  10.20 (s, 1H), 9.39 (s, 1H), 8.72 (s, 1H), 8.04 (d, J=2.0 Hz, 1H), 7.93 (d, J=9.2 Hz, 1H), 7.82 (dd, J=2.0, 8.0 Hz, 1H), 7.67 (dd, J=2.0, 9.0 Hz, 1H), 7.50 (d, J=8.0 Hz, 1H), 4.92 (s, 2H), 2.66 (s, 3H), 2.36 (s, 3H), 2.23 (s, 3H), 2.18 (s, 3H). MS  $m/z$  485.18 (M+1)<sup>+</sup>.

Synthesis of 6-carbamothioyl-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (169)

**[0566]**



-continued



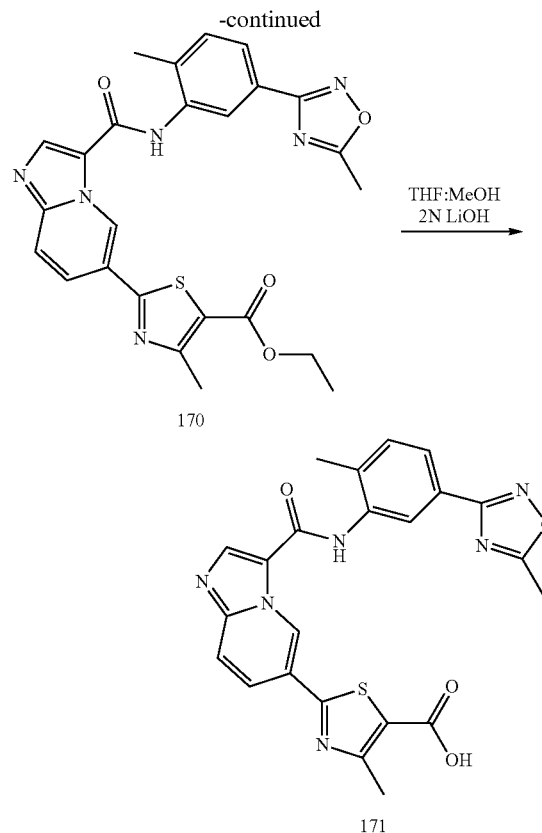
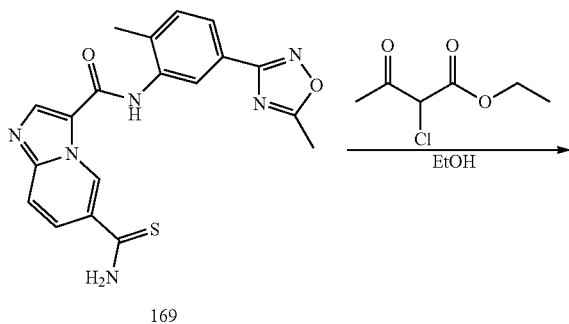
**[0567]** To a stirring solution of ethyl 6-cyanoimidazo[1,2-a]pyridine-3-carboxylate (24q) (500 mg, 2.32 mmol) and thioacetamide (524 mg, 6.97 mmol) in anhydrous N,N-dimethylformamide (3 mL) was added 4N HCl in dioxane (1 mL). The reaction was heated at 100° C. for 5 h. The reaction was cooled to room temperature. The reaction was diluted with water and the pH was adjusted to between 6-8 with a saturated solution of sodium bicarbonate. The crude product was extracted with ethyl acetate. The organic was washed with 2 $\times$  water/brine mixture and dried over anhydrous sodium sulfate. The crude 6-carbamothioylimidazo[1,2-a]pyridine-3-carboxylate (167) was obtained as a yellow solid (400 mg, 69%) and was used in the next step without further purification. <sup>1</sup>H NMR (400 MHz,  $d_6$ -DMSO)  $\delta$  10.15 (s, 1H), 9.91 (dd, J=0.9, 1.9 Hz, 1H), 9.83 (s, 1H), 8.37 (s, 1H), 7.99 (dd, J=1.9, 9.4 Hz, 1H), 7.82 (dd, J=0.9, 9.4 Hz, 1H), 4.39 (q, J=7.1 Hz, 2H), 1.36 (t, J=7.1 Hz, 3H). MS  $m/z$  249.06 (M+1)<sup>+</sup>.

**[0568]** To a stirring solution of ethyl 6-carbamothioylimidazo[1,2-a]pyridine-3-carboxylate (167) (500 mg, 2.01 mmol) in THF:MeOH (4:1, 5 mL) was added 2N LiOH (1 mL). The reaction was heated at 60° C. for 30 minutes. The reaction was cooled to room temperature and quenched with 10% citric acid (pH 4-5). The solvent was partially reduced. The resulting solid was collected by vacuum filtration to obtain 6-carbamothioylimidazo[1,2-a]pyridine-3-carboxylic acid (168) as a yellow solid (250 mg, 56%). The crude product was used in the next step without further purification. <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.13 (s, 1H), 9.92 (dd, J=0.9, 1.9 Hz, 1H), 9.81 (s, 1H), 8.31 (d, J=3.6 Hz, 1H), 7.95 (dd, J=1.9, 9.5 Hz, 1H), 7.79 (dd, J=0.9, 9.4 Hz, 1H). MS m/z 221.03 (M+1)<sup>+</sup>.

**[0569]** A mixture of 6-carbamothioylimidazo[1,2-a]pyridine-3-carboxylic acid (168) (25 mg, 0.113 mmol), 2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)aniline (33) (21 mg, 0.113 mmol) and 1-propanephosphonic acid cyclic anhydride solution 50 wt. % in ethyl acetate (135 uL, 0.226 mmol) in ethyl acetate (1 mL) were heated at 65° C. for 6 h. The reaction was cooled to room temperature and diluted with a saturated solution of sodium bicarbonate. The crude product was extracted with ethyl acetate. The organic was washed with 2× water, 1× brine and dried over anhydrous sodium sulfate. The solvent was concentrated. The crude product was taken in dichloromethane and methanol. The resulting solid was collected by vacuum filtration to obtain 6-carbamothioyl-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (169) as a yellow solid (211 mg, 43%). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.12 (s, 1H), 10.11-10.10 (m, 1H), 10.09 (s, 1H), 9.79 (s, 1H), 8.65 (s, 1H), 8.10 (d, J=1.7 Hz, 1H), 7.96 (dd, J=1.9, 9.5 Hz, 1H), 7.83-7.76 (m, 2H), 7.50 (d, J=8.1 Hz, 1H), 2.67 (s, 3H), 2.37 (s, 3H). MS m/z 392.11 (M+1)<sup>+</sup>.

Synthesis of 4-methyl-2-(3(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-5-carboxylic acid (171)

**[0570]**

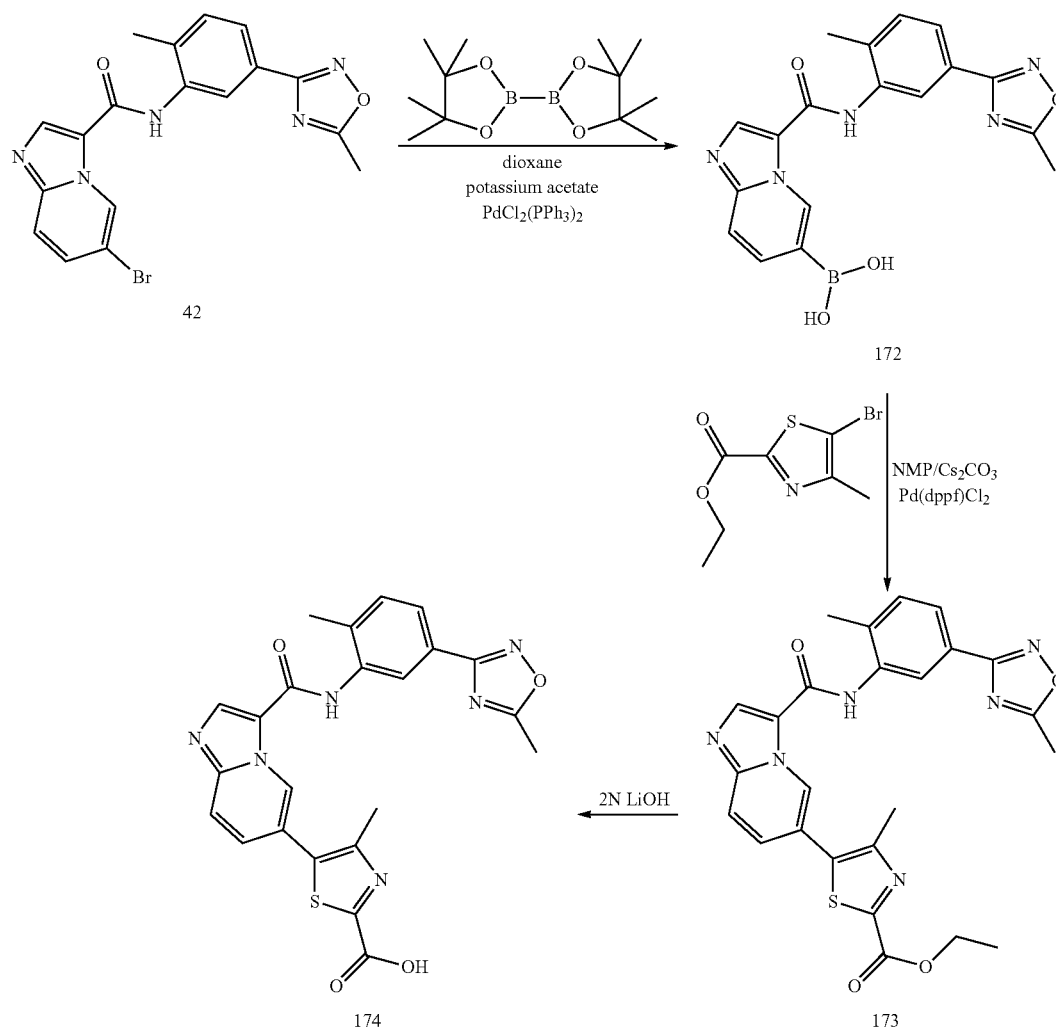


**[0571]** A stirring suspension of 6-carbamothioyl-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (169) (100 mg, 0.255 mmol) and ethyl 2-chloroacetoacetate (71 uL, 0.51 mmol) in ethanol (4 mL) was refluxed overnight. Another 2 eq of ethyl 2-chloroacetoacetate was added and the reaction was reflux. The solvent was concentrated and the crude product was purified by silica chromatography to obtain a tan solid (170) (90 mg, 70%). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.19 (dd, J=0.9, 1.8 Hz, 1H), 10.17 (s, 1H), 8.67 (s, 1H), 8.10 (d, J=1.7 Hz, 1H), 8.02 (dd, J=1.9, 9.4 Hz, 1H), 7.91 (dd, J=0.9, 9.4 Hz, 1H), 7.82 (dd, J=1.8, 7.9 Hz, 1H), 7.51 (d, J=8.1 Hz, 1H), 4.31 (q, J=7.1 Hz, 2H), 2.72 (s, 3H), 2.67 (s, 3H), 2.38 (s, 3H), 1.31 (t, J=7.1 Hz, 3H). MS m/z 502.14 (M+1)<sup>+</sup>.

**[0572]** To a stirring solution of ethyl 4-methyl-2-(3(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-5-carboxylate (170) (88 mg, 0.175 mmol) in THF:MeOH (4:1, 2 mL) was added 2N LiOH (0.8 mL). The reaction was heated at 55° C. for 30 minutes. The reaction was cooled to room temperature and quenched with 10% citric acid. The solvent was partially reduced. The resulting solid was collected by vacuum filtration to obtain a tan solid (171) (65 mg, 78%). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.19-10.15 (m, 2H), 8.66 (s, 1H), 8.09 (d, J=1.7 Hz, 1H), 8.01 (dd, J=1.9, 9.4 Hz, 1H), 7.91 (dd, J=0.9, 9.4 Hz, 1H), 7.82 (dd, J=1.7, 7.9 Hz, 1H), 7.51 (d, J=8.1 Hz, 1H), 6.56 (s, 1H), 2.70 (s, 3H), 2.67 (s, 3H), 2.38 (s, 3H). MS m/z 474.11 (M+1)<sup>+</sup>.

Synthesis of 4-methyl-5-(34(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-2-carboxylic acid (174)

[0573]



[0574] A mixture of 6-bromo-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (42) (250 mg, 0.606 mmol), 4,4',4',5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (154 mg, 0.606 mmol), dichloro-bis(triphenylphosphine)palladium (21 mg, 0.030 mmol) and potassium acetate (149 mg, 1.52 mmol) in anhydrous dioxane (6 mL) was heated in the microwave at 130° C. for 20 minutes. The reaction was filtered through celite. The solvent was concentrated and the crude product was purified by silica chromatography to obtain (3-((2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)boronic acid (172) as a tan solid (150 mg, 66%). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.09 (s, 1H), 9.80 (s, 1H), 8.64 (s, 1H), 8.10 (d, J=1.7 Hz, 1H), 7.89 (d, J=9.0 Hz, 1H), 7.80 (dd, J=5.3, 13.1 Hz, 2H), 7.50 (d, J=8.1 Hz, 1H), 2.67 (s, 3H), 2.37 (s, 3H). MS m/z 377.13 (M+1)<sup>+</sup>.

[0575] A mixture of (3-((2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)

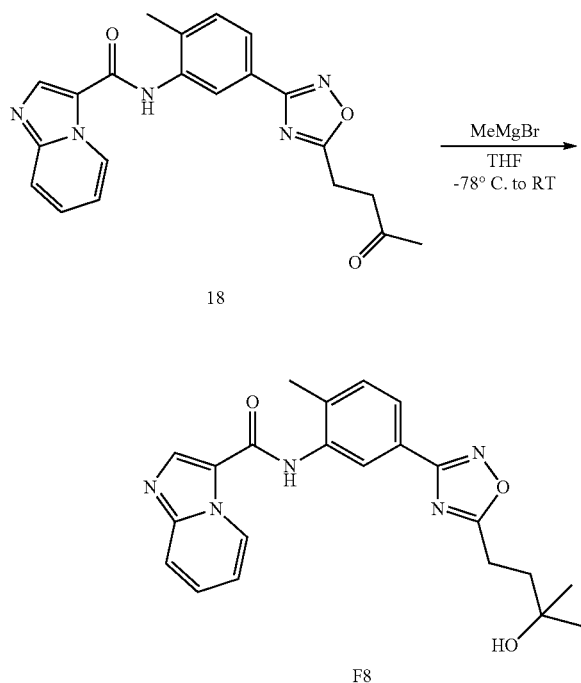
boronic acid (172) (300 mg, 0.795 mmol), ethyl 5-bromo-4-methylthiazole-2-carboxylate (199 mg, 0.795 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (58 mg, 0.080 mmol) and cesium carbonate (311 mg, 0.955 mmol) in anhydrous NMP (2.5 mL) was heated in the microwave at 130° C. for 20 minutes. The crude product was taken in ethyl acetate and water. The organic layer was washed with 2× water/brine mixture and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography to obtain ethyl 4-methyl-5-(3-((2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-2-carboxylate (173) as an oil (650 mg, 81%). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.17 (s, 1H), 9.70 (dd, J=0.9, 1.9 Hz, 1H), 8.68 (s, 1H), 8.06 (d, J=1.7 Hz, 1H), 7.94 (dd, J=0.9, 9.3 Hz, 1H), 7.81 (dd, J=1.8, 7.9 Hz, 1H), 7.75 (dd, J=1.9, 9.3 Hz, 1H), 7.50 (d, J=8.0 Hz, 1H), 4.38 (t, J=7.1 Hz, 2H), 2.66 (s, 3H), 2.55 (s, 3H), 2.36 (s, 3H), 1.34 (t, J=7.1 Hz, 3H). MS m/z 502.14 (M+1)<sup>+</sup>.

**[0576]** To a stirring solution of ethyl 4-methyl-5-(3-((2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-2-carboxylate (173) (300 mg, 0.597 mmol) in THF:MeOH (4:1, 3 mL) was added 2N LiOH (0.5 mL). The reaction was stirred at room temperature for 30 minutes. The pH was adjusted between 4-5 with 10% citric acid. The product was collected by filtration to obtain 4-methyl-5-(3-((2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-2-carboxylic acid (174) as a tan solid (169 mg, 95%). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.11 (s, 1H), 9.59 (s, 1H), 8.63 (s, 1H), 8.05 (s, 1H), 7.86 (d, J=9.4, 1H), 7.81 (dd, J=1.7, 7.9 Hz, 1H), 7.63 (dd, J=1.8, 9.3 Hz, 1H), 7.49 (d, J=8.0 Hz, 1H), 2.66 (s, 3H), 2.43 (s, 3H), 2.36 (s, 3H). MS m/z 474.11 (M+1)<sup>+</sup>.

#### Synthesis of Final Compounds

##### Synthesis of N-(5-(5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F8)

**[0577]**

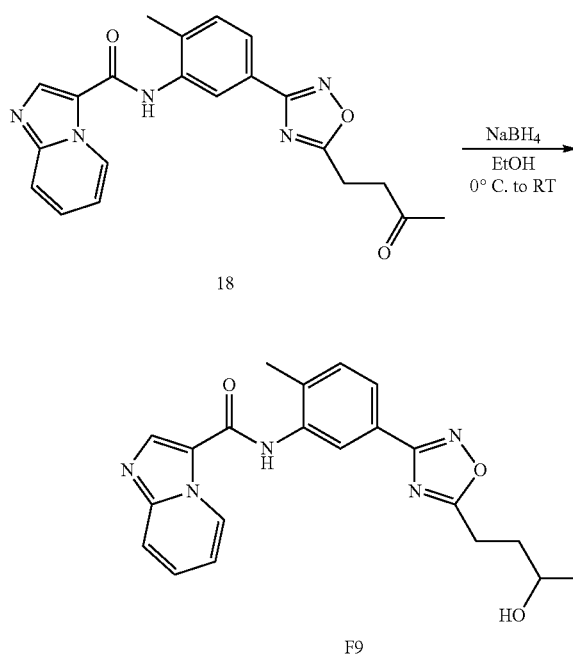


**[0578]** To a stirring solution of N-(2-methyl-5-(5-(3-oxobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (18) (150 mg, 0.385 mmol) in anhydrous THF at -78°C under argon was added dropwise a solution of methylmagnesium bromide (435 μL, 1.3 mmol). The reaction was stirred at room temperature for 30 minutes, then cooled to 0°C and quenched with 1N HCl. The crude product was extracted with ethyl acetate, washed with 1N HCl, water,

brine and dried over sodium sulfate. The crude product was purified by silica chromatography to yield N-(5-(5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F8). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.12 (s, 1H), 9.50 (d, J=6.8 Hz, 1H), 8.66 (s, 1H), 8.04 (s, 1H), 8.06 (d, J=0.8 Hz, 1H), 7.80-7.87 (m, 2H), 7.63 (t, J=8.0 Hz, 1H), 7.49 (d, J=8 Hz, 1H), 7.26 (t, J=6.8 Hz, 1H), 3.01-3.35 (m, 2H), 2.36 (s, 3H), 1.85-1.91 (m, 2H), 1.14 (s, 6H). MS m/z 406.45 (M+1)<sup>+</sup>.

##### Synthesis of N-(5-(5-(3-hydroxybutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F9)

**[0579]**

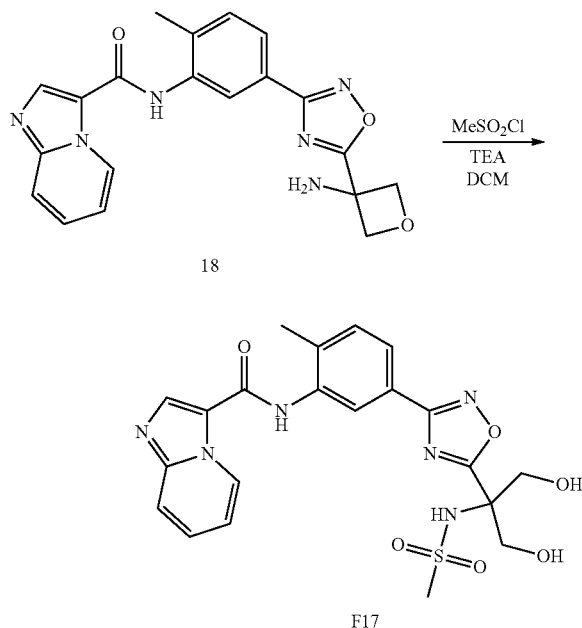


**[0580]** To a stirring suspension of N-(2-methyl-5-(5-(3-oxobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (18) (100 mg, 0.257 mmol) in EtOH (3 mL) at 0°C was added sodium borohydride (12 mg, 0.308 mmol). The reaction was stirred to room temperature for 15 minutes. Then, the reaction was cooled to 0°C and quenched with water. The crude reaction was purified by reverse phase preparative HPLC to give N-(5-(5-(3-hydroxybutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F9). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.15 (s, 1H), 9.51 (d, J=6.9, 1H), 8.69 (s, 1H), 8.07 (s, 1H), 7.85 (dd, J=8.5, 19.0, 2H), 7.66 (s, 1H), 7.50 (d, J=8.1, 1H), 7.29 (s, 1H), 3.60-3.70 (m, 2H), 2.96-3.10 (m, 2H), 2.37 (s, 3H), 1.77-1.98 (m, 2H), 1.11 (d, J=6.2, 3H). MS m/z 392.42 (M+1)<sup>+</sup>.



Synthesis of N-(5-(5-(1,3-dihydroxy-2-(methylsulfonylamido)propan-2-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F17)

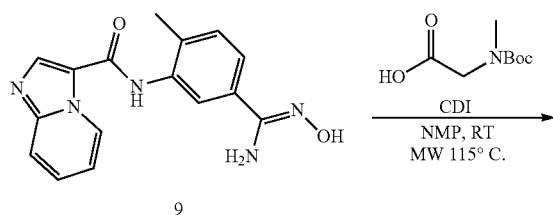
[0581]



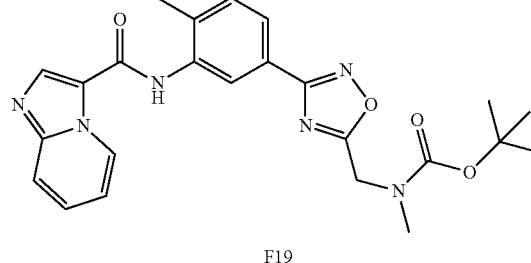
[0582] To a stirring solution of N-(5-(5-(3-aminooxetan-3-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (47) (8.0 mg, 0.02 mmol) and triethylamine (4.1 mg, 0.04 mmol) in anhydrous dichloromethane (1 mL) was added methanesulfonyl chloride (3.5 mg, 0.03 mmol). The reaction was stirred to room temperature for 10 minutes. The solvent was removed and the crude was purified by preparative HPLC to afford N-(5-(5-(1,3-dihydroxy-2-(methylsulfonylamido)propan-2-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F17). MS  $m/z$  487.1 (M+1)<sup>+</sup>.

Synthesis of tert-butyl (3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methyl(methyl)carbamate (F19)

[0583]



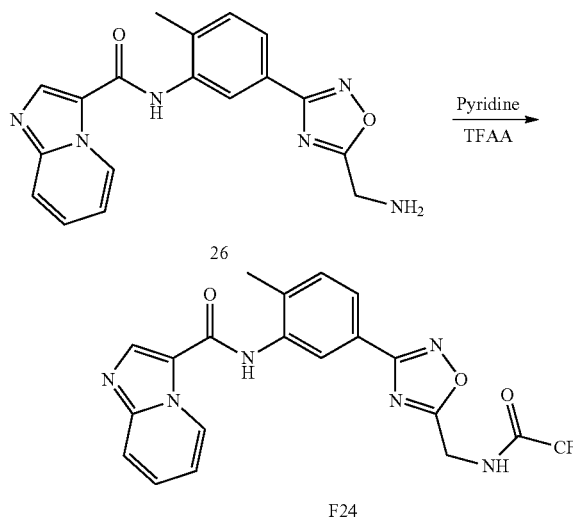
-continued



[0584] To a stirring solution of 2-(tert-butoxycarbonyl(methyl)amino)acetic acid (122 mg, 0.647 mmol) in anhydrous NMP (1.5 mL) was added 1,1'-carbonyldiimidazole (CDI) (105 mg, 0.647 mmol). The reaction was stirred for 2 minutes. N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9) (100 mg, 0.323 mmol) was added and the reaction was stirred for 15 minutes, then heated via microwave at 120° C. for 15 minutes. The crude was purified by preparative HPLC to give tert-butyl (3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methyl(methyl)carbamate (F19). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.17 (s, 1H), 9.52-9.48 (m, 1H), 8.68 (s, 1H), 8.06 (d, J=1.6 Hz, 1H), 7.88-7.85 (m, 1H), 7.84-7.81 (m, 1H), 7.67-7.63 (m, 1H), 7.51 (d, J=8.0 Hz, 1H), 7.31-7.26 (m, 1H), 4.78-4.76 (m, 2H), 2.99 (s, 3H), 2.37 (s, 3H), 1.28 (s, 9H). MS  $m/z$  463.50 (M+1)<sup>+</sup>.

Synthesis of N-(2-methyl-5-(5-((2,2,2-trifluoroacetamido)methyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F24)

[0585]

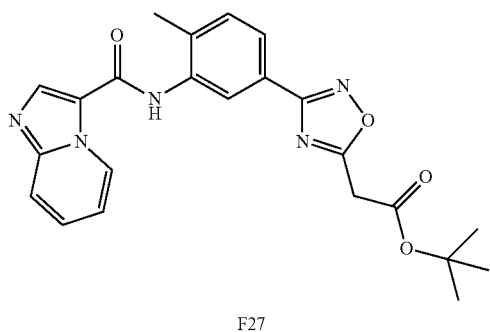
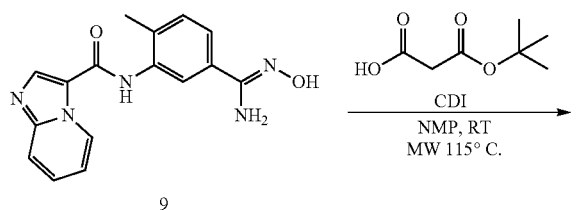


[0586] To a stirring solution of N-(5-(5-(aminomethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide hydrochloride (26) (50 mg, 0.130 mmol) in anhydrous pyridine (1 mL) was added trifluoroacetic anhydride (36 μL, 0.260 mmol). The reaction was stirred at room temperature for 1 hour. The crude product was purified by preparative HPLC yielding N-(2-methyl-5-(5-((2,2,2-trifluoro-

roacetamido)methyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F24). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.43 (s, 1H), 10.15 (s, 1H), 9.50 (d, J=7.0 Hz, 1H), 8.67 (s, 1H), 8.06 (s, 1H), 7.93-7.79 (m, 2H), 7.64 (s, 1H), 7.52 (d, J=8.1 Hz, 1H), 7.28 (s, 1H), 4.84 (d, J=5.6 Hz, 2H), 2.37 (s, 3H). MS m/z 445.37 (M+1)<sup>+</sup>.

Synthesis of tert-butyl 2-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)acetate (F27)

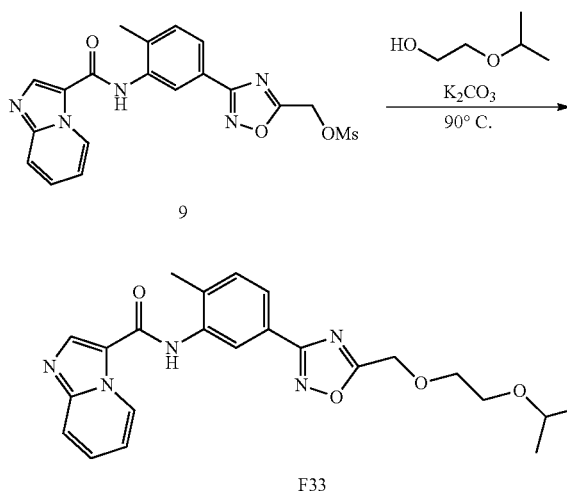
[0587]



[0588] To a stirring solution of 3-tert-butoxy-3-oxopropanoic acid (518 mg, 1.62 mmol) in anhydrous NMP (2 mL) was added 1,1'-carbonyldiimidazole (CDI) (295 mg, 1.21 mmol). The reaction was stirred for 2 minutes. N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9) (250 mg, 0.808 mmol) was added and the reaction was stirred for 25 minutes, then heated via microwave at 115°C for 10 minutes. The crude product was purified by preparative HPLC to yield tert-butyl 2-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)acetate (F27). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.18 (s, 1H), 9.53-9.51 (m, 1H), 8.71 (s, 1H), 8.10 (d, J=1.6 Hz, 1H), 7.90-7.87 (m, 1H), 7.83 (dd, J=1.6, 8.0 Hz, 1H), 7.71-7.67 (m, 1H), 7.52 (d, J=8.0 Hz, 1H), 7.34-7.30 (m, 1H), 4.27 (s, 2H), 2.38 (s, 3H), 1.43 (s, 9H). MS m/z 434.18 (M+1)<sup>+</sup>.

Synthesis of N-(5-(5-((2-isopropoxyethoxy)methyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F33)

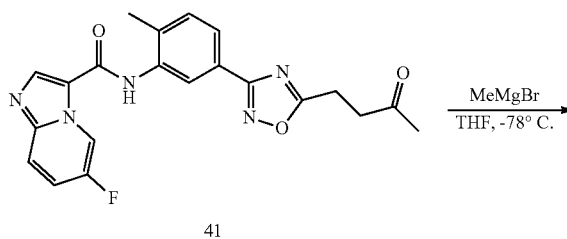
[0589]

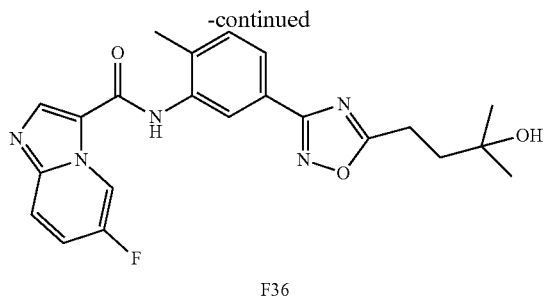


[0590] A mixture of (3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methyl methanesulfonate (44) (8.5 mg, 0.02 mmol) and K<sub>2</sub>CO<sub>3</sub> (8.3 mg, 0.06 mmol) in neat 2-isopropoxyethanol (0.5 mL) was heated at 90°C for 30 minutes. The reaction mixture was purified by preparative HPLC to afford N-(5-(5-((2-isopropoxyethoxy)methyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F33). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.47 (m, 1H), 8.50 (d, J=1.5 Hz, 1H), 8.13 (s, 1H), 7.81 (dd, J=1.7 Hz, 7.9, 1H), 7.68 (d, J=9.0 Hz, 1H), 7.57 (s, 1H), 7.37 (ddd, J=1.3, 6.8, 9.0 Hz, 1H), 7.31 (d, J=8.0 Hz, 1H), 6.97 (td, J=1.1, 6.9 Hz, 1H), 4.83 (s, 2H), 3.80-3.67 (m, 2H), 3.6-3.50 (m, 3H), 2.36 (s, 3H), 1.11 (d, J=6.0 Hz, 6H). MS m/z 436.2 (M+1)<sup>+</sup>.

Synthesis of 6-fluoro-N-(5-(5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F36)

[0591]

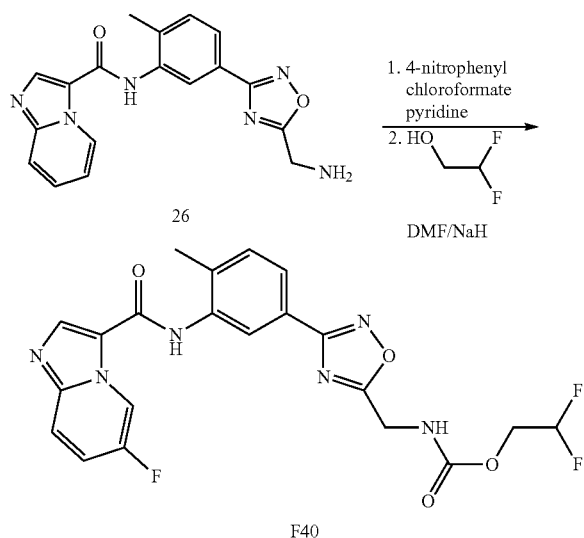




**[0592]** 6-Fluoro-N-(2-methyl-5-(5-(3-oxobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (41) (0.1 g, 0.24 mmol) in THF (2 mL) was added dropwise to a stirred and cooled ( $-78^{\circ}\text{C}$ .) THF solution of MeMgBr (0.6 mmol). After the addition, the solution was warmed to  $0^{\circ}\text{C}$ . and after 30 minutes quenched with  $\text{NH}_4\text{Cl}$ . After aqueous workup, the residue was purified by reverse phase HPLC to give 6-fluoro-N-(5-(5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F36).  $^1\text{H}$  NMR (400 MHz,  $d_4$ -MeOH)  $\delta$  9.67-9.66 (m, 1H), 8.67 (s, 1H), 8.11 (s, 1H), 7.94-7.89 (m, 2H), 7.83-7.78 (m, 1H), 7.48 (d,  $J=8$  Hz, 1H), 3.08 (dd,  $J=8.0, 6.4$  Hz, 2H), 2.45 (s, 3H), 2.03 (dd,  $J=8.0, 6.4$  Hz, 2H), 1.27 (s, 6H). MS  $m/z$  424.1 (M+1) $^+$ .

Synthesis of 2,2-difluoroethyl ((3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methyl)carbamate (F40)

**[0593]**

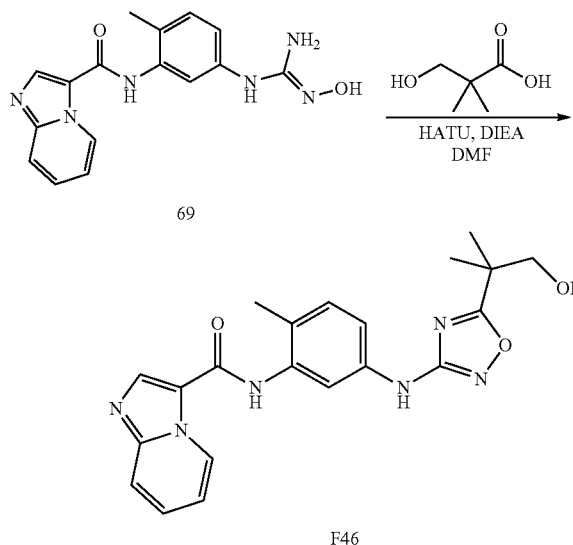


**[0594]** To a stirring suspension of N-(5-(5-(aminomethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide hydrochloride (26) (500 mg, 1.30 mmol) in anhydrous pyridine (10 mL) at room temperature was added 4-nitrophenyl chloroformate (275 mg, 1.36 mmol). The reaction was stirred under Argon for 4 hours at room temperature. The solvent was concentrated and the crude product was purified by silica chromatography to yield 4-Nitrophenyl ((3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methyl)carbamate, which was immediately use in the next reaction. MS  $m/z$  514.14 (M+1) $^+$ .

**[0595]** To a stirring solution of 2,2-difluoroethanol (48 mg, 0.584 mmol) in anhydrous DMF (2 mL) at  $0^{\circ}\text{C}$ . was added sodium hydride (60%, 29 mg, 0.730 mmol). The reaction mixture was stirred to room temperature under Argon for 20 minutes. 4-Nitrophenyl ((3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methyl)carbamate (150 mg, 0.292 mmol) dissolved in N,N-dimethylformamide (1 mL) was added. The reaction mixture was stirred at room temperature for 15 minutes. The reaction mixture was quenched with water, filtered and the crude product was purified by reverse phase preparative HPLC to give 2,2-difluoroethyl ((3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methyl)carbamate (F40).  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO)  $\delta$  10.11 (s, 1H), 9.51-9.46 (m, 1H), 8.65 (s, 1H), 8.44 (t,  $J=6.0$  Hz, 1H), 8.07 (d,  $J=1.2$  Hz, 1H), 7.85-7.08 (m, 2H), 7.63-7.59 (m, 1H), 7.51 (d,  $J=8.0$  Hz, 1H), 7.27-7.24 (m, 1H), 6.39-6.10 (m, 1H), 4.61 (d,  $J=5.6$  Hz, 2H), 4.35-4.27 (m, 2H), 2.37 (s, 3H). MS  $m/z$  457.14 (M+1) $^+$ .

Synthesis of N-(5-(5-(1-hydroxy-2-methylpropan-2-yl)-1,2,4-oxadiazol-3-ylamino)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F46)

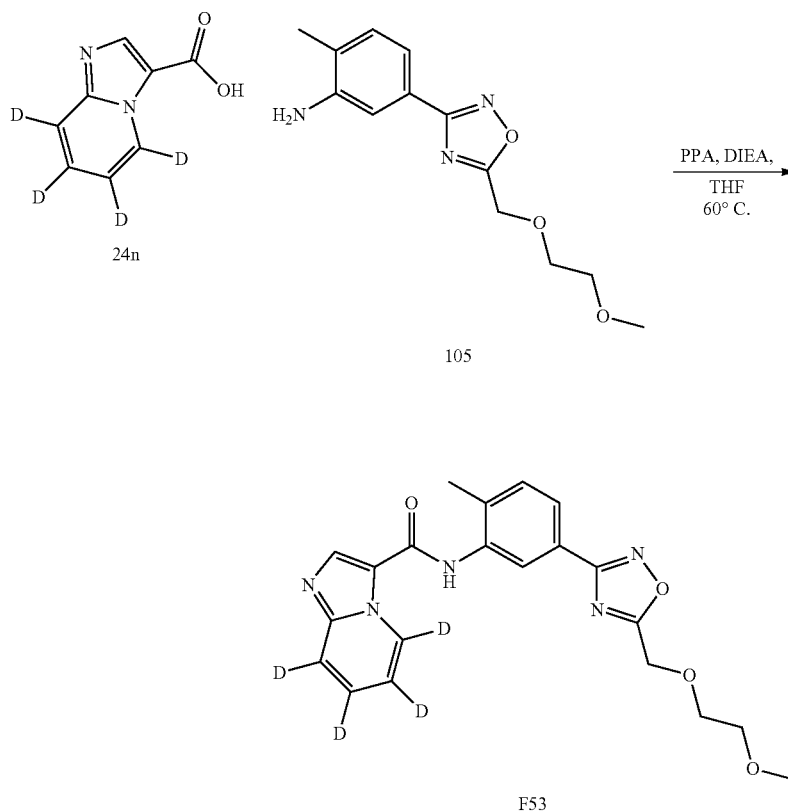
**[0596]**



**[0597]** To a solution of 3-hydroxy-2,2-dimethylpropanoic acid (1.11 g, 9.4 mmol) and HATU (3.59 g, 9.4 mmol) in DMF (80 mL) was added DIPEA (1.66 mL, 10.4 mmol). The mixture was stirred at room temperature for 10 minutes then N-(5-(2-hydroxyguanidino)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (69) (3.05 g, 9.4 mmol) was added in portions and stirred for 30 minutes followed by addition of DMF (80 mL). The diluted mixture was then stirred for 4 hours at  $100^{\circ}\text{C}$ . After cooling to room temperature the mixture was poured into water (300 mL) and extracted with EtOAc (300 mL $\times$ 3). The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , concentrated and purified by column chromatography (0% to 5% MeOH in dichloromethane as eluant) to afford the desired product N-(5-(5-(1-hydroxy-2-methylpropan-2-yl)-1,2,4-oxadiazol-3-ylamino)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F46) which was recrystallized in dichloromethane to yield a white solid.  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO)  $\delta$  10.30 (s, 1H), 9.86 (s, 1H), 9.55 (d,  $J=6.8$  Hz, 1H), 8.86 (s, 1H), 7.95 (d,  $J=9.5$  Hz, 1H), 7.87-7.83 (m, 1H), 7.45-7.41 (m, 2H), 7.23 (dd,  $J=8.0, 2.0$  Hz, 1H), 7.17 (d,  $J=8.4$  Hz, 1H), 3.48 (s, 2H), 2.13 (s, 3H), 1.24 (s, 6H). MS  $m/z$  407.2 (M+1) $^+$ .

Synthesis of N-(5-(5-((2-methoxyethoxy)methyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)5,6,7,8,deuteroimidazo[1,2-a]pyridine-3-carboxamide (F53)

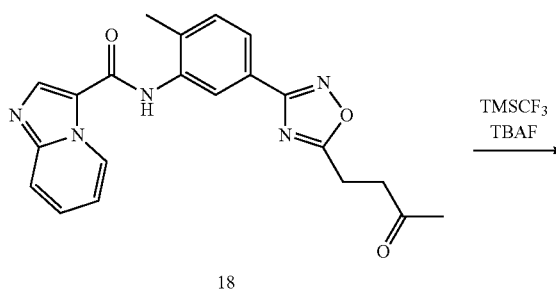
[0598]

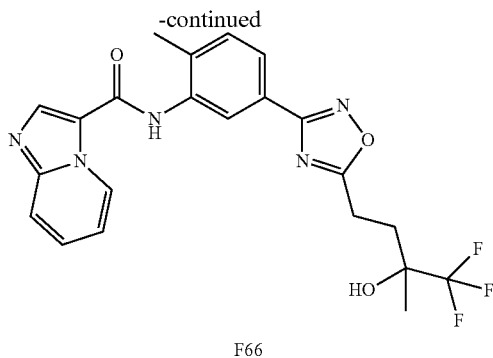


[0599] 5,6,7,8,Deutero-imidazo[1,2-a]pyridine-3-carboxylic acid (24n) (0.2 g, 1.20 mmol), 5-(5-((2-methoxyethoxy)methyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (0.38 g, 1.44 mmol) (105), propylphosphonic anhydride solution (2.5 mL, 50% in EtOAc), and DIEA (0.5 mL, 4.6 mmol) in THF (20 mL) was heated at 60° C. for 5 hours. Saturated NaHCO<sub>3</sub> solution was then added to quench the reaction and the mixture was partitioned between EtOAc and water. The organic phase was washed with saturated NH<sub>4</sub>Cl solution and dried over MgSO<sub>4</sub>. The crude product was purified over silica gel using 10% MeOH in dichloromethane to obtain N-(5-(5-((2-methoxyethoxy)methyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)5,6,7,8,deutero-imidazo[1,2-a]pyridine-3-carboxamide (F53) as a solid. <sup>1</sup>H NMR (400 MHz, d<sub>4</sub>-MeOH) δ 8.49 (s, 1H), 8.14 (m, 1H), 7.92 (d, J=4.0 Hz, 1H), 7.48 (d, J=4.0 Hz, 1H), 4.90 (s, 2H), 3.82 (m, 2H), 3.62 (m, 2H), 3.36 (s, 3H), 2.42 (s, 3H). MS m/z 412.2 (M+1)<sup>+</sup>

Synthesis of N-(2-methyl-5-(5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F66)

[0600]





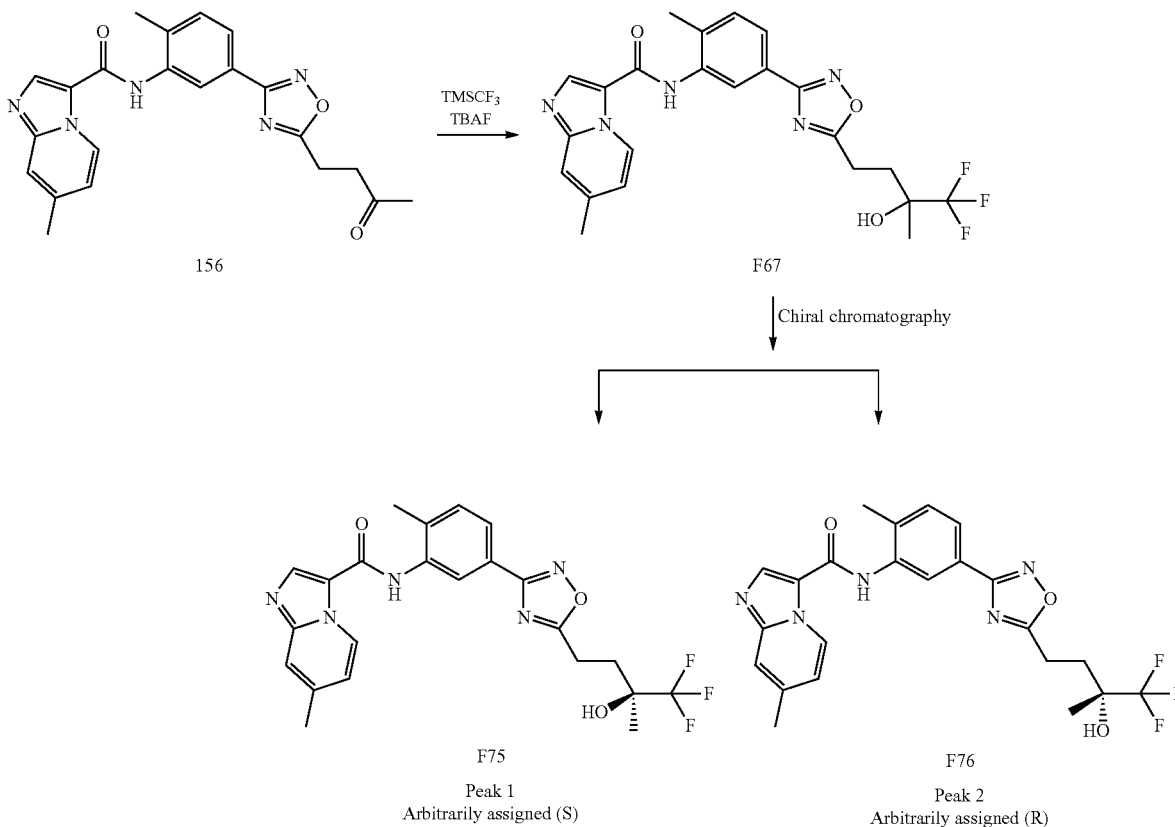
**[0601]** To a solution of N-(2-methyl-5-(5-(3-oxobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (18) (200 mg, 0.51 mmol) and TBAF (0.5 M in THF and 5% water, 2.2 mL) in anhydrous THF (1.5 mL) at 0° C. was added trifluoromethyltrimethylsilane dropwise (excess) and the reaction was stirred to room temperature for 15 minutes. The reaction was checked by LCMS. More trifluoromethyltrimethylsilane was added dropwise until the reac-

tion was complete by LCMS. Then another batch of TBAF (0.5 M in THF and 5% water, 2.2 mL) was added and the reaction was stirred for 30 minutes. The solvent was concentrated and the crude product was dissolved in ethyl acetate. The organic phase was washed with a water/brine solution followed by brine and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography to yield N-(2-methyl-5-(5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F66). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 9.98 (s, 1H), 9.40 (d, J=6.8 Hz, 1H), 8.54 (s, 1H), 8.01 (d, J=1.6 Hz, 1H), 7.75 (m, 2H), 7.42-7.48 (m, 2H), 7.12 (dt, J=0.8, 6.8 Hz, 1H), 6.04 (s, 1H), 3.07 (m, 2H), 2.31 (s, 3H), 1.98-2.17 (m, 2H), 1.25 (s, 3H). MS m/z 460.1 (M+1)<sup>+</sup>.

Synthesis of 7-methyl-N-(2-methyl-5-(5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F67, F75 and F76)

Method A:

**[0602]**

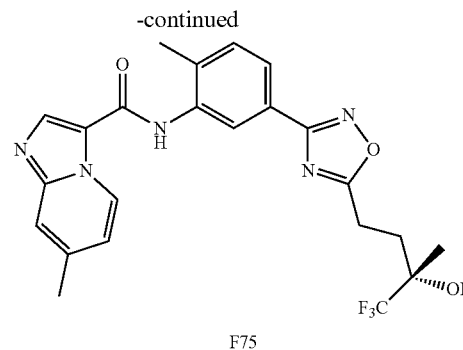
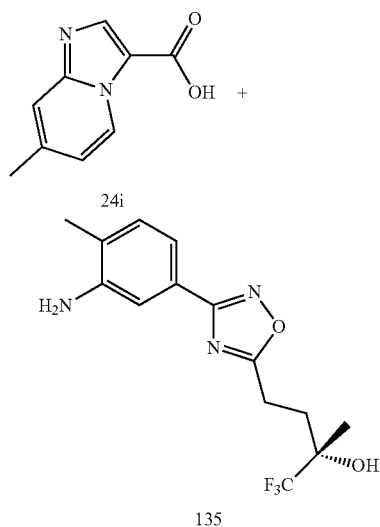


**[0603]** To a solution of N-(2-methyl-5-(5-(3-oxobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (156) (3.04 g, 7.52 mmol) and TBAF (1 M in THF, 15 mL) in anhydrous THF (50 mL) at  $-20^{\circ}\text{C}$ . was added trifluoromethyltrimethylsilane dropwise (16 ml, 108 mmol) and the reaction was stirred to room temperature for 30 minutes. Then another batch of TBAF (1 M in THF, 8 mL) was added and the reaction was stirred for 30 minutes. The solvent was concentrated and the crude product was dissolved in ethyl acetate. The organic phase was washed with a water/brine solution followed by brine and dried over anhydrous sodium sulfate. The solvent was removed under vacuum to yield a residue. To the above residue was added DCM (20 mL) and the mixture was sonicated for 5 minutes. The precipitate was filtered and dried in air to give 7-methyl-N-(2-methyl-5-(5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F67).  $^1\text{H NMR}$  (400 MHz,  $d_6$ -DMSO)  $\delta$  9.96 (s, 1H), 9.32 (d,  $J=7.2$  Hz, 1H), 8.52 (s, 1H), 8.07 (d,  $J=1.6$  Hz, 1H), 7.81 (dd,  $J=1.6, 8.0$  Hz, 1H), 7.04 (dd,  $J=1.6, 7.2$  Hz, 1H), 6.11 (s, 1H), 3.14 (m, 2H), 2.43 (s, 3H), 2.36 (s, 3H), 2.04-2.24 (m, 2H), 1.32 (s, 3H). MS  $m/z$  474.1 (M+1) $^+$ .

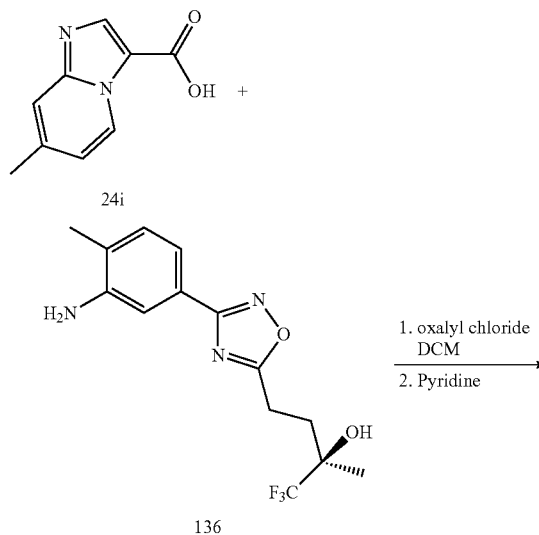
**[0604]** The separation of F67 was performed by VWR LAprep P110+P130+P314 using Chiralpak IC 20  $\mu\text{m}$  column (4 $\times$ SMB 5 $\times$ 20 cm) at a flow rate of 80 ml/min, using DCM/ethanol (90:10). Analytical methods using the Chiralpak IC 5  $\mu\text{m}$  column and the same solvent mixture showed peak 1 eluting at 6.73 min, and peak 2 at 10.77 min. Peak 1 was arbitrarily assigned to be the isomer of (S)-7-methyl-N-(2-methyl-5-(5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F75) and Peak 2 was assigned to be the isomer of (R)-7-methyl-N-(2-methyl-5-(5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F76).  $^1\text{H NMR}$  (400 MHz,  $d_6$ -DMSO)  $\delta$  9.96 (s, 1H), 9.32 (d,  $J=7.2$  Hz, 1H), 8.52 (s, 1H), 8.07 (d,  $J=1.6$  Hz, 1H), 7.81 (dd,  $J=1.6, 8.0$  Hz, 1H), 7.04 (dd,  $J=1.6, 7.2$  Hz, 1H), 6.11 (s, 1H), 3.14 (m, 2H), 2.43 (s, 3H), 2.36 (s, 3H), 2.04-2.24 (m, 2H), 1.32 (s, 3H). MS  $m/z$  474.1 (M+1) $^+$ .

Method B:

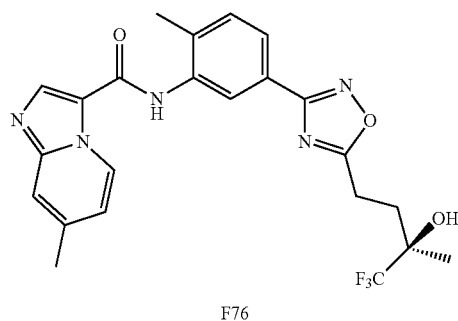
**[0605]**



**[0606]** To a stirring suspension of 7-methylimidazo[1,2-a]pyridine-3-carboxylic acid (24i) (300 mg, 1.71 mmol) in anhydrous dichloromethane (3 mL) was added dropwise oxalyl chloride (0.45 mL, 5.1 mmol). Then, a drop of anhydrous DMF was added and the reaction mixture was stirred at room temperature for 1 hour. The solvent was concentrated and the crude solid was added to a stirring solution of (S)-4-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)-1,1,1-trifluoro-2-methylbutan-2-ol (135) (467 mg, 1.48 mmol) in anhydrous pyridine (3 mL) at room temperature. The reaction was stirred at room temperature for 20 minutes. Then water (10 mL) was added and stirred for 10 minutes. The precipitate was filtered, washed with water and dried in air. To the above solid, DCM (2 mL) was added and the resulting suspension was sonicated for 2 minutes. The solid was filtered, washed with small amount of DCM and dried in air to yield a white solid of (S)-7-methyl-N-(2-methyl-5-(5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F75).  $^1\text{H NMR}$  (400 MHz,  $d_6$ -DMSO)  $\delta$  9.96 (s, 1H), 9.32 (d,  $J=7.2$  Hz, 1H), 8.52 (s, 1H), 8.07 (d,  $J=1.6$  Hz, 1H), 7.81 (dd,  $J=1.6, 8.0$  Hz, 1H), 7.04 (dd,  $J=1.6, 7.2$  Hz, 1H), 6.11 (s, 1H), 3.14 (m, 2H), 2.43 (s, 3H), 2.36 (s, 3H), 2.04-2.24 (m, 2H), 1.32 (s, 3H). MS  $m/z$  474.1 (M+1) $^+$ .



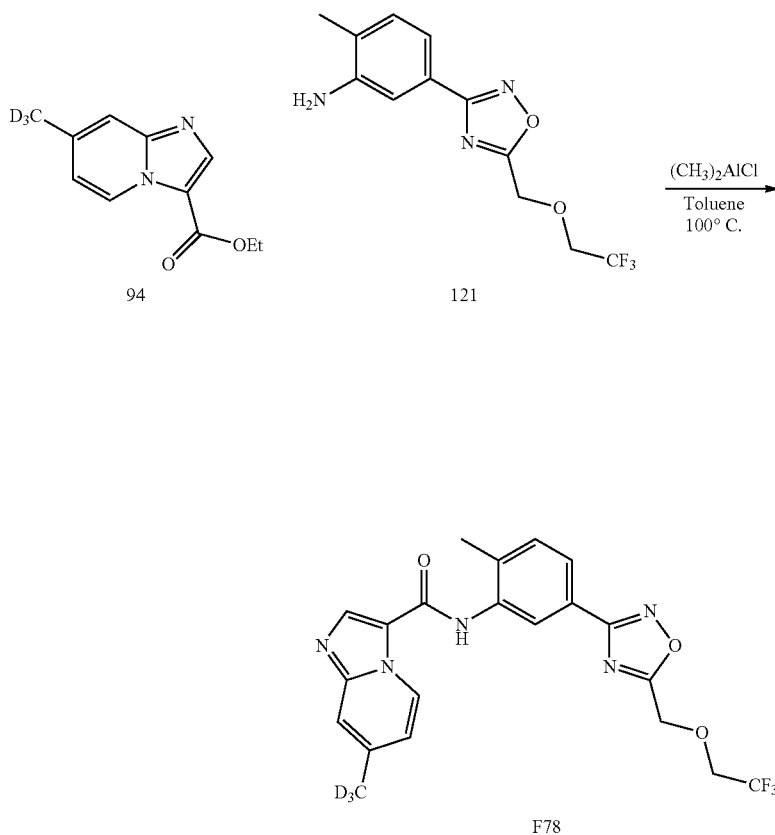
-continued



**[0607]** To a stirring suspension of 7-methylimidazo[1,2-a]pyridine-3-carboxylic acid (24i) (300 mg, 1.71 mmol) in anhydrous dichloromethane (3 mL) was added dropwise oxalyl chloride (0.45 mL, 5.1 mmol). Then, a drop of anhydrous DMF was added and the reaction mixture was stirred at room temperature for 1 hour. The solvent was concentrated

and the crude solid was added to a stirring solution of (R)-4-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)-1,1,1-trifluoro-2-methylbutan-2-ol (136) (467 mg, 1.48 mmol) in anhydrous pyridine (3 mL) at room temperature. The reaction was stirred at room temperature for 20 minutes. Then water (10 mL) was added and stirred for 10 minutes. The precipitate was filtered, washed with water and dried in air. To the above solid, DCM (2 mL) was added and the resulting suspension was sonicated for 2 minutes. The solid was filtered, washed with small amount of DCM and dried in air to yield a white solid of (R)-7-methyl-N-(2-methyl-5-(5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F76). <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 9.96 (s, 1H), 9.32 (d, J=7.2 Hz, 1H), 8.52 (s, 1H), 8.07 (d, J=1.6 Hz, 1H), 7.81 (dd, J=1.6, 8.0 Hz, 1H), 7.04 (dd, J=1.6, 7.2 Hz, 1H), 6.11 (s, 1H), 3.14 (m, 2H), 2.43 (s, 3H), 2.36 (s, 3H), 2.04-2.24 (m, 2H), 1.32 (s, 3H). MS m/z 474.1 (M+1)<sup>+</sup>.

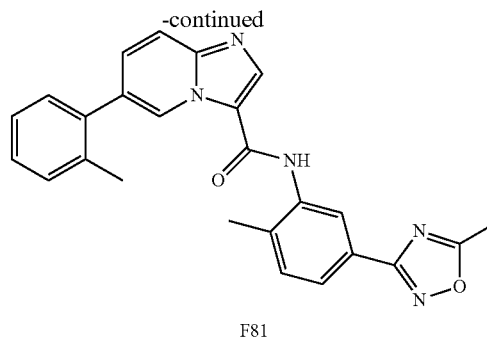
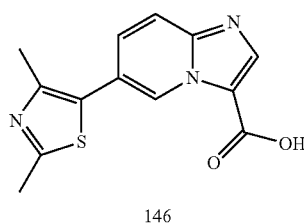
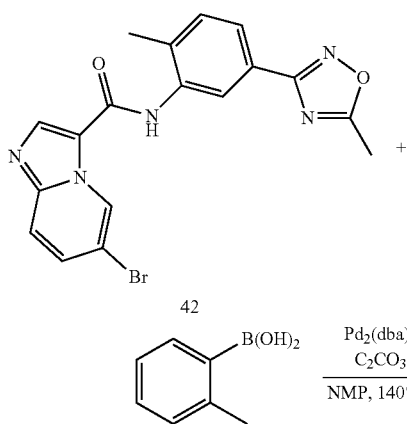
Synthesis of 7-methyl-d3-N-(2-methyl-5-(5-((2,2,2-trifluoroethoxy)methyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F78)

**[0608]**

**[0609]** To a stirring solution of 2-methyl-5-(5-((2,2,2-trifluoroethoxy)methyl)-1,2,4-oxadiazol-3-yl)aniline (121) (348 mg, 1.21 mmol) in anhydrous toluene (4 mL) was added dimethylaluminum chloride (1.2 mL, 1.21 mmol). The reaction was stirred at room temperature for 1 hour. Then, ethyl 7-methyl- $d_3$ -imidazo[1,2-a]pyridine-3-carboxylate (94) (78 mg, 0.378 mmol) was added and the reaction was heated at 100° C. for 1.5 hours. The reaction mixture was quenched with water and the solvent was concentrated. The crude product was purified by reverse phase preparative HPLC to afford 7-methyl- $d_3$ -N-(2-methyl-5-(5-((2,2,2-trifluoroethoxy)methyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F78).  $^1\text{H NMR}$  (400 MHz,  $d_6$ -DMSO)  $\delta$  9.97 (s, 1H), 9.33 (d,  $J=7.2$  Hz, 1H), 8.54 (bs, 1H), 8.11 (d,  $J=1.6$  Hz, 1H), 7.84 (dd,  $J=1.6, 7.6$  Hz, 1H), 7.58 (s, 1H), 7.51 (d,  $J=8.0$  Hz, 1H), 7.04 (d,  $J=8.4$  Hz, 1H), 5.12 (s, 2H), 4.36 (q,  $J=8.8$  Hz, 2H), 2.37 (s, 3H). MS  $m/z$  449.1 (M+1) $^+$ .

Synthesis of N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)-6-(*o*-tolyl)imidazo[1,2-a]pyridine-3-carboxamide (F81)

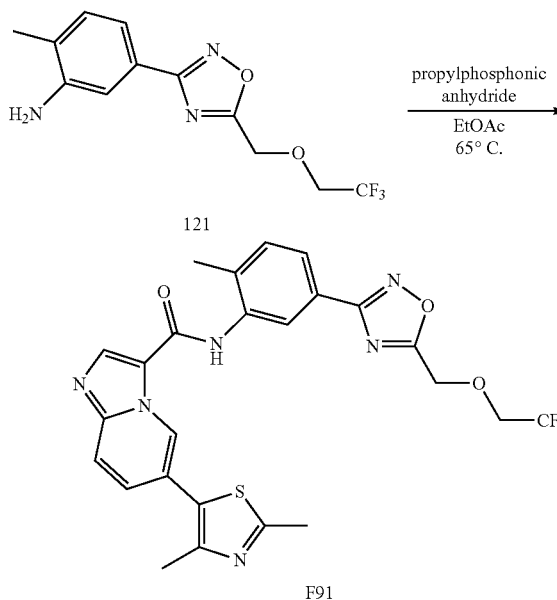
**[0610]**



**[0611]** A mixture of 6-bromo-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (42) (25 mg, 0.061 mmol), *o*-tolylboronic acid (12 mg, 0.091 mmol), [(*t*-Bu) $_3$ PH]BF $_4$  (3 mg, 0.009 mmol), tris(dibenzylideneacetone)dipalladium (0) (3 mg, 0.003 mmol) and cesium carbonate (30 mg, 0.091 mmol) in anhydrous 1-methyl-2-pyrrolidinone (1 mL) was heated in the microwave at 140° C. for 10 minutes. The reaction was filtered through celite. The crude product was taken in water and ethylacetate. The organic was washed with water/brine mixture and dried over anhydrous sodium sulfate. The crude product was purified by reverse phase preparative HPLC to afford N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)-6-(*o*-tolyl)imidazo[1,2-a]pyridine-3-carboxamide (F81).  $^1\text{H NMR}$  (400 MHz,  $d_6$ -DMSO)  $\delta$  10.12 (s, 1), 9.42 (s, 1H), 8.68 (s, 1H), 8.06 (d,  $J=1.6$  Hz, 1H), 7.87 (d,  $J=9.2$  Hz, 1H), 7.79 (dd,  $J=1.6, 8.0$  Hz, 1H), 7.64 (dd,  $J=1.6, 9.2$  Hz, 1H), 7.48 (d,  $J=8.0$  Hz, 1H), 7.37-7.31 (m, 4H), 2.65 (s, 3H), 2.36 (s, 3H), 2.28 (s, 3H). MS  $m/z$  423.17 (M+1) $^+$ .

Synthesis of 6-(2,4-dimethylthiazol-5-yl)-N-(2-methyl-5-(5-((2,2,2-trifluoroethoxy)methyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F91)

**[0612]**

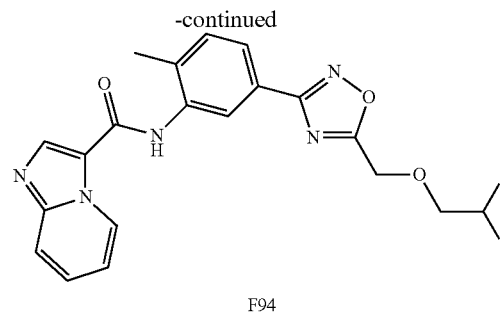
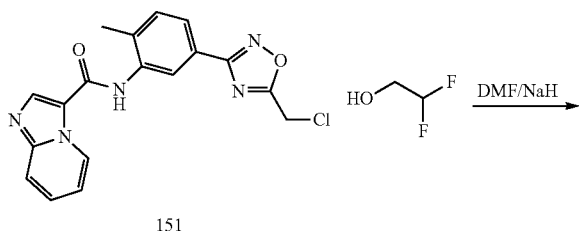




**[0613]** To a stirring suspension of 6-(2,4-dimethylthiazol-5-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (146) (25 mg, 0.091 mmol) and 2-methyl-5-(5-((2,2,2-trifluoroethoxy)methyl)-1,2,4-oxadiazol-3-yl)aniline (121) (26 mg, 0.091 mmol) in ethylacetate (1 mL) was added propylphosphonic anhydride solution 50 wt. % in ethyl acetate (109  $\mu$ L, 0.183 mmol). The reaction was heated at 65° C. overnight. The reaction was cooled to room temperature and diluted with a solution of saturated sodium bicarbonate. The organic was separated and washed with 2 $\times$  water/brine mixture and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography to afford 6-(2,4-dimethylthiazol-5-yl)-N-(2-methyl-5-(5-((2,2,2-trifluoroethoxy)methyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F91). <sup>1</sup>H NMR (400 MHz, d<sub>4</sub>-MeOD)  $\delta$  10.12 (s, 1H), 9.57 (s, 1H), 8.64 (s, 1H), 8.09 (d, J=1.6 Hz, 1H), 7.89-7.83 (m, 2H), 7.60 (dd, J=2.0, 9.6 Hz, 1H), 7.52 (d, J=8.0 Hz, 1H), 5.12 (s, 2H), 4.39-4.32 (m, 2H), 2.65 (s, 3H), 2.41 (s, 3H), 2.37 (s, 3H). MS m/z 542.13 (M+1)<sup>+</sup>.

Synthesis of N-(5-(5-((2,2-difluoroethoxy)methyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F94)

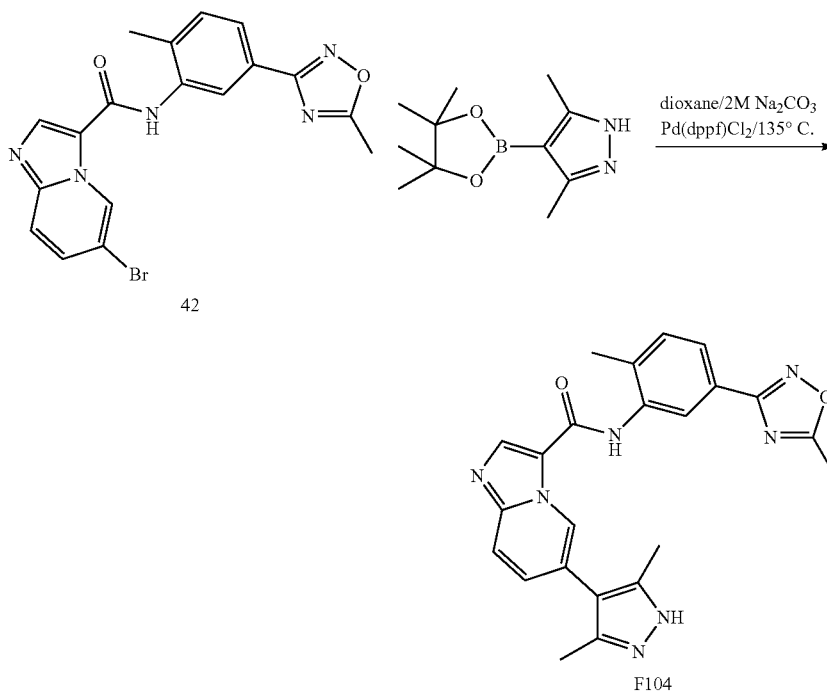
**[0614]**



**[0615]** To a stirring solution of 2,2-difluoroethanol (33 mg, 0.408 mmol) in anhydrous N,N-dimethylformamide (1 mL) at 0° C. was added sodium hydride (60%, 20 mg, 0.510 mmol). The reaction mixture was stirred to room temperature under Argon for 20 minutes. Then, N-(5-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (151) (75 mg, 0.204 mmol) dissolved in 0.5 mL of N,N-dimethylformamide was added and the reaction was stirred for 30 minutes. The reaction was quenched with water and filtered. The crude product was purified by silica chromatography to give N-(5-(5-(2,2-difluoroethoxy)methyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F94). <sup>1</sup>H NMR (400 MHz, d<sub>4</sub>-MeOD)  $\delta$  10.15 (s, 1H), 9.52-9.49 (m, 1H), 8.67 (s, 1H), 8.10 (d, J=1.6 Hz, 1H), 7.87-7.84 (m, 2H), 7.67-7.62 (m, 1H), 7.52 (d, J=8.4 Hz, 1H), 7.30-7.26 (m, 1H), 6.40-6.10 (m, 1H), 5.04 (s, 2H), 3.99-3.91 (m, 2H), 2.38 (s, 3H). MS m/z 414.13 (M+1)<sup>+</sup>.

Synthesis of 6-(3,5-dimethyl-1H-pyrazol-4-yl)-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F104)

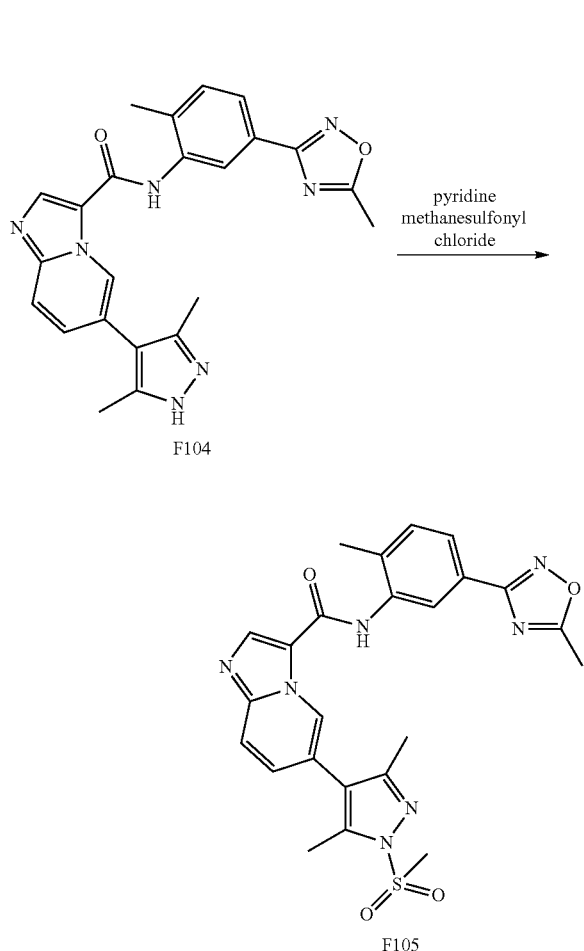
**[0616]**



**[0617]** A mixture of 6-bromo-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (42) (100 mg, 0.243 mmol), 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (81 mg, 0.364 mmol), [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II) (18 mg, 0.024 mmol) and a solution of 2M sodium carbonate (300  $\mu$ L) in anhydrous dioxane (1.5 mL) was heated in the microwave at 135° C. for 20 minutes. The cooled reaction was diluted with water and the solid was collected by vacuum filtration. The product was purified by silica chromatography to give 6-(3,5-dimethyl-1H-pyrazol-4-yl)-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide as a tan solid (F104). <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO)  $\delta$  10.14 (s, 1H), 9.40 (s, 1H), 8.67 (s, 1H), 8.03 (d, *J*=1.6 Hz, 1H), 7.89 (dd, *J*=0.8, 9.2 Hz, 1H), 7.81 (dd, *J*=2.0, 8.0 Hz, 1H), 7.65-7.62 (m, 1H), 7.49 (d, *J*=8.0 Hz, 1H), 2.66 (s, 3H), 2.35 (s, 3H), 2.24 (s, 6H). MS *m/z* 428.18 (M+1)<sup>+</sup>.

Synthesis of 6-(3,5-dimethyl-1-(methylsulfonyl)-1H-pyrazol-4-yl)-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F105)

**[0618]**

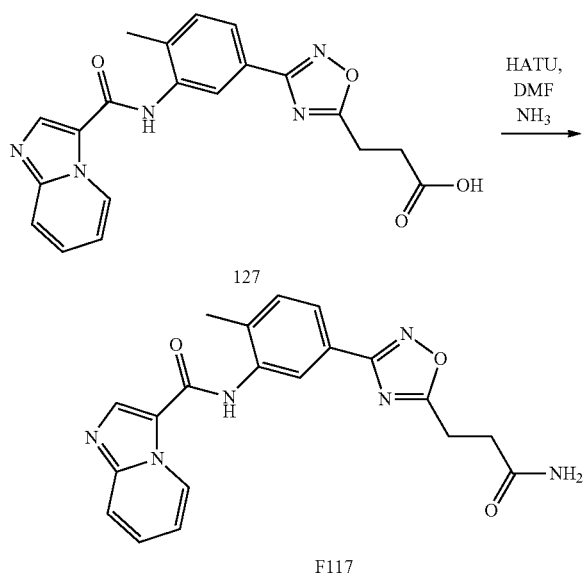


**[0619]** To a stirring solution of 6-(3,5-dimethyl-1H-pyrazol-4-yl)-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)

phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F104) (64 mg, 0.150 mmol) in anhydrous pyridine (1 mL) at 0° C. under Argon was added methanesulfonyl chloride (23  $\mu$ L, 0.117 mmol). The reaction was stirred to room temperature for 20 minutes. The crude product was purified by reverse phase preparative HPLC to give 6-(3,5-dimethyl-1-(methylsulfonyl)-1H-pyrazol-4-yl)-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F105) as a tan solid. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO)  $\delta$  10.16 (s, 1H), 9.44 (s, 1H), 8.70 (s, 1H), 8.07 (d, *J*=1.6 Hz, 1H), 7.94 (dd, *J*=0.8, 9.2 Hz, 1H), 7.80 (dd, *J*=1.6, 7.6 Hz, 1H), 7.61 (dd, *J*=2.0, 9.6 Hz, 1H), 7.49 (d, *J*=8.0 Hz, 1H), 3.54 (s, 3H), 2.66 (s, 3H), 2.45 (s, 3H), 2.36 (s, 3H), 2.22 (s, 3H). MS *m/z* 506.15 (M+1)<sup>+</sup>.

Synthesis of N-(5-(5-(3-amino-3-oxopropyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F117)

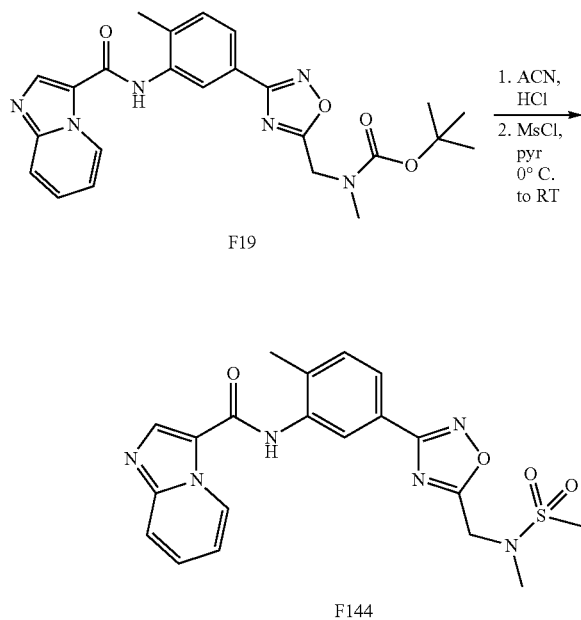
**[0620]**



**[0621]** To a stirring solution of 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)propanoic acid (127) (25 mg, 0.0639 mmol) in anhydrous DMF (1 mL) was added HATU (29 mg, 0.0767 mmol). The reaction was stirred at room temperature for 5 minutes. Then, 7 N ammonia in MeOH (150  $\mu$ L) was added and the reaction was stirred for 6 hours. The crude product was purified by preparative HPLC to yield N-(5-(5-(3-amino-3-oxopropyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F117). <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO)  $\delta$  10.16 (s, 1H), 9.51 (d, *J*=7.2 Hz, 1H), 8.69 (s, 1H), 8.05 (s, 1H), 7.84 (d, *J*=9.2 Hz, 1H), 7.82 (dd, *J*=7.6, 1.6 Hz, 1H), 7.64-7.84 (m, 1H), 7.50 (d, *J*=8 Hz, 1H), 7.29 (t, *J*=7.2 Hz, 1H), 6.94 (s, 1H), 3.15 (t, *J*=7.2 Hz, 2H), 2.68 (t, *J*=7.2 Hz, 2H), 2.36 (s, 3H). MS *m/z* 391.40 (M+1)<sup>+</sup>.

Synthesis of N-(2-methyl-5-(5-(N-methylmethylsulfonamido)methyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F144)

[0622]

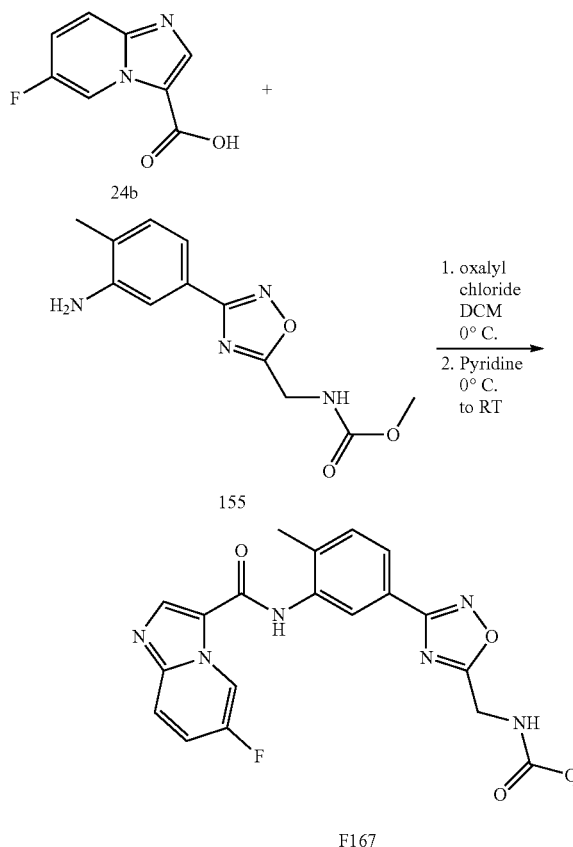


**[0623]** To a stirring suspension of tert-butyl (3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methyl(methyl)carbamate (F19) (90 mg, 0.195 mmol) in  $\text{CH}_3\text{CN}$  (1 mL) was added HCl (4N in dioxane, 1 mL) and water (0.5 mL). The reaction mixture was stirred at room temperature for 45 minutes and concentrated under high vacuum. The crude product N-(2-methyl-5-(5-((methylamino)methyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide hydrochloride was used in the next step without further purification.

**[0624]** To a stirring suspension of N-(2-methyl-5-(5-((methylamino)methyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide hydrochloride (39 mg, 0.0973 mmol) in anhydrous pyridine (1 mL) at  $0^\circ\text{C}$ . was added methanesulfonyl chloride (8  $\mu\text{L}$ , 0.0973 mmol). The reaction was stirred to room temperature for 5 minutes. The reaction was quenched with water and the crude product was purified by preparative HPLC to yield N-(2-methyl-5-(5-((N-methylmethylsulfonamido)methyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F144).  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO)  $\delta$  10.16 (s, 1H), 9.52-9.49 (m, 1H), 8.68 (s, 1H), 8.09 (d,  $J=1.6$  Hz, 1H), 7.87-7.84 (m, 2H), 7.67-7.63 (m, 1H), 7.52 (d,  $J=8.0$  Hz, 1H), 7.30-7.26 (m, 1H), 4.80 (s, 2H), 3.07 (s, 3H), 2.96 (s, 3H), 2.37 (s, 3H). MS  $m/z$  441.48 ( $\text{M}+1$ ) $^+$ .

Synthesis of methyl (3-(3-(6-fluoroimidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methylcarbamate (F167)

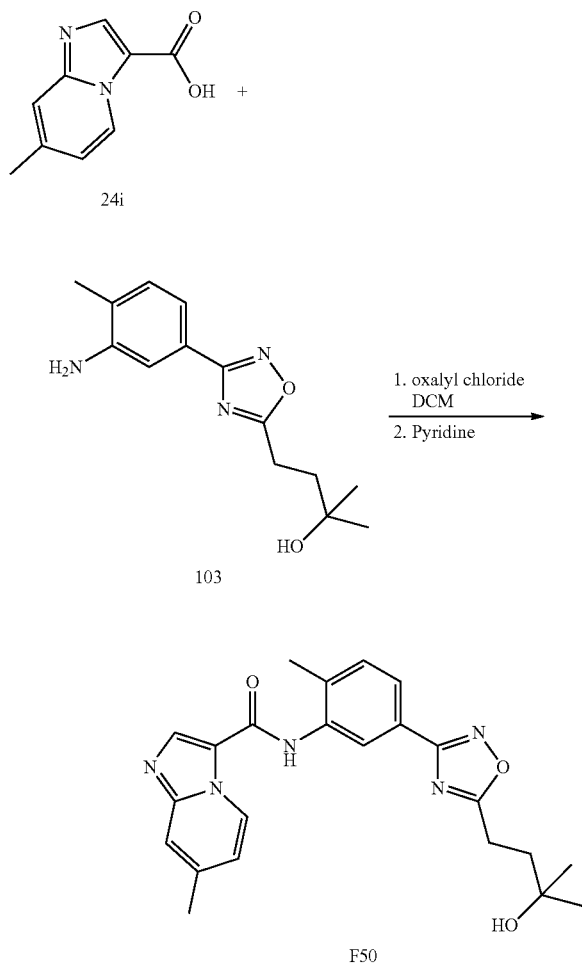
[0625]



**[0626]** To a stirring suspension of 6-fluoroimidazo[1,2-a]pyridine-3-carboxylic acid (24b) (150 mg, 0.833 mmol) in anhydrous dichloromethane (3 mL) at  $0^\circ\text{C}$ . under argon was added dropwise oxalyl chloride (74  $\mu\text{L}$ , 0.874 mmol). Then, a drop of anhydrous DMF was added and the reaction mixture was stirred at  $0^\circ\text{C}$ . for 1.5 hours. The solvent was concentrated and the crude solid was added to a stirring solution of methyl (3-(3-(6-fluoroimidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methylcarbamate (F167).  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO)  $\delta$  10.12 (s, 1H), 9.48-9.46 (m, 1H), 8.63 (s, 1H), 8.07 (t,  $J=5.6$  Hz, 1H), 8.06 (d,  $J=1.6$  Hz, 1H), 7.90-7.86 (m, 1H), 7.82 (dd,  $J=2.0, 8.0$  Hz, 1H), 7.67-7.62 (m, 1H), 7.50 (d,  $J=8.0$  Hz, 1H), 4.57 (d,  $J=6.0$  Hz, 2H), 3.59 (s, 3H), 2.36 (s, 3H). MS  $m/z$  425.39 ( $\text{M}+1$ ) $^+$ .

Synthesis of N-(5-(5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide (F50)

[0627]

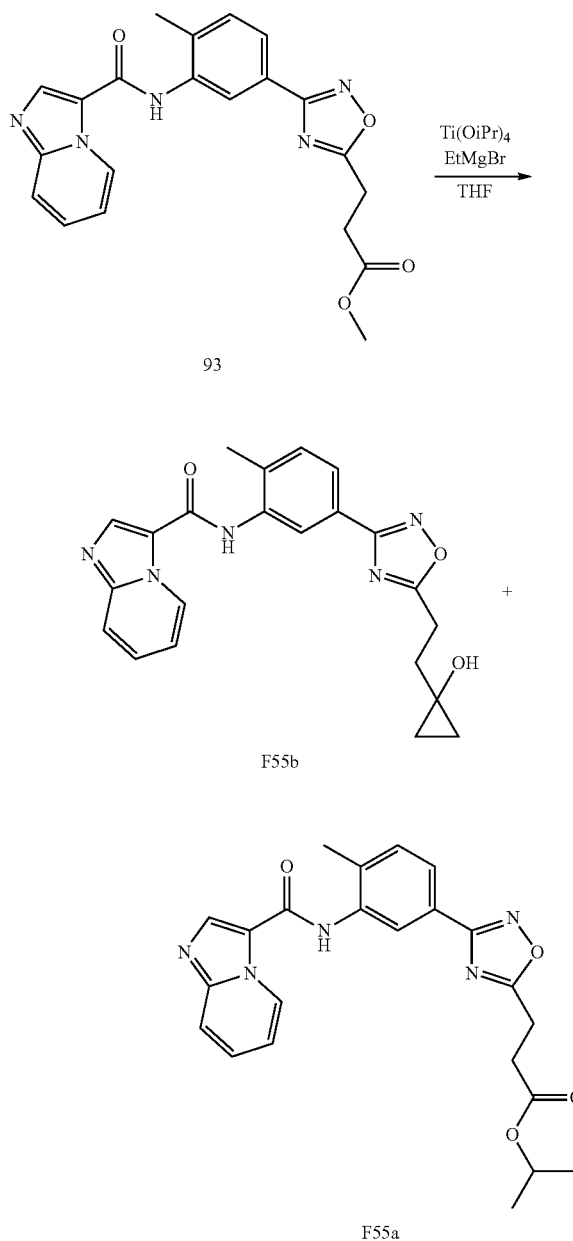


[0628] To a stirring suspension of 7-methylimidazo[1,2-a]pyridine-3-carboxylic acid (24i) (145 mg, 0.823 mmol) in anhydrous dichloromethane (3 mL) was added dropwise oxalyl chloride (0.22 mL, 2.47 mmol). Then, a drop of anhydrous DMF was added and the reaction mixture was stirred at room temperature for 1 hour. The solvent was concentrated and the crude solid was added to a stirring solution of 4-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)-2-methylbutan-2-ol (103) (180 mg, 0.69 mmol) in anhydrous pyridine (3 mL) at room temperature. The reaction was stirred at room temperature for 20 minutes. Then water (10 mL) was added and stirred for 10 minutes. The precipitate was filtered and dried in air. Recrystallization by EtOAc gave a white solid of N-(5-(5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide (F50). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.41 (d,

J=7.2 Hz, 1H), 8.56 (d, J=1.6 Hz, 1H), 8.15 (s, 1H), 7.86 (dd, J=1.6, 7.6 Hz, 1H), 7.57 (s, 1H), 7.52 (s, 1H), 7.38 (d, J=8.0 Hz, 1H), 6.89 (dd, J=1.6, 7.2 Hz, 1H), 3.11 (m, 2H), 2.49 (s, 3H), 2.43 (s, 3H), 2.09 (m, 2H), 1.74 (s, 1H), 1.34 (s, 6H). MS m/z 420.2 (M+1)<sup>+</sup>.

Synthesis of N-(5-(5-(2-(1-hydroxycyclopropylethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F55a)

[0629]



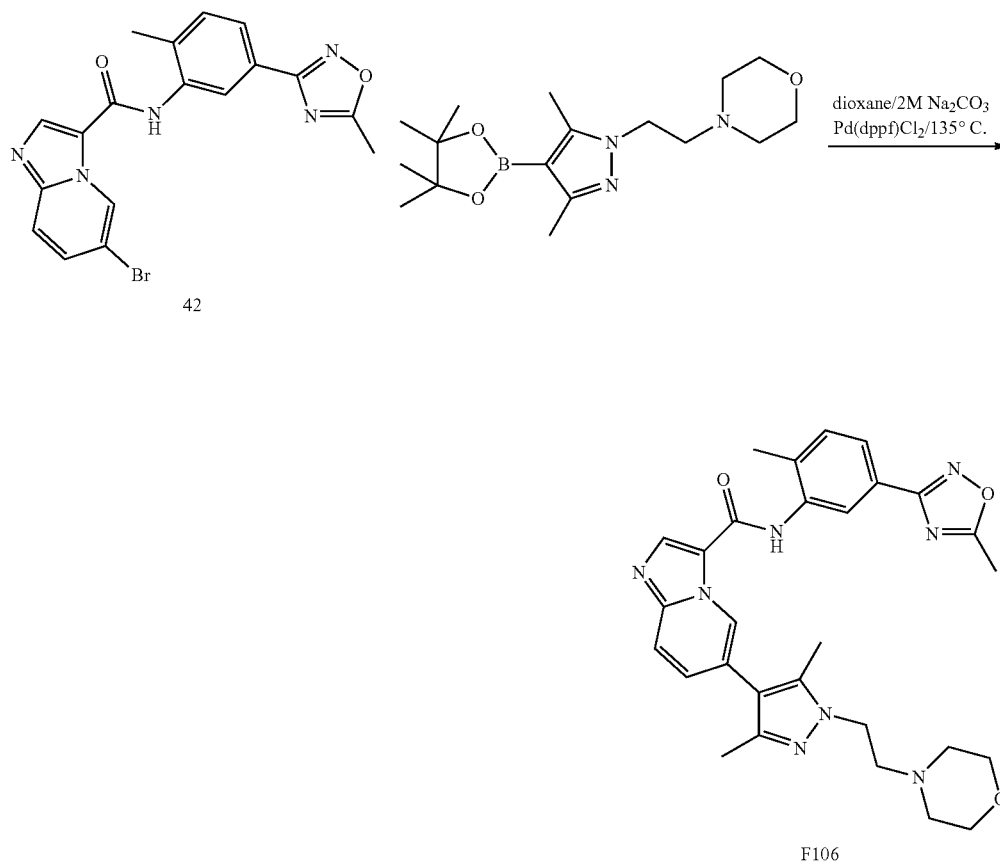
**[0630]** To a stirring solution of methyl 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)propanoate (93) (100 mg, 0.25 mmol) in anhydrous THF at  $-15^{\circ}\text{C}$ . under argon was added dropwise a solution of ethylmagnesium bromide (247 L, 0.74 mmol). The reaction was stirred at room temperature for 16 hours. The reaction was quenched with saturated  $\text{NH}_4\text{Cl}$ . The crude product was extracted with ethyl acetate, washed with water and brine and dried over sodium sulfate. The crude product was purified by preparative HPLC to to yield both N-(5-(2-(1-hydroxycyclopropyl)ethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F55b) and isopropyl 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)propanoate (F55a).  $^1\text{H}$  NMR for (F55b) (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  9.89 (d,  $J=6.8$  Hz, 1H), 9.81 (s, 1H), 9.56 (s, 1H), 8.21 (s, 1H),

8.19 (d,  $J=8.0$  Hz, 1H), 8.0 (t,  $J=8.0$  Hz, 1H), 7.88 (dd,  $J=1.6, 7.6$  Hz, 1H), 7.53 (t,  $J=7.2$  Hz, 1H), 7.42 (d,  $J=8.0$  Hz, 1H), 3.23 (t,  $J=7.2$  Hz, 2H), 2.47 (s, 3H), 2.12 (t,  $J=7.2$  Hz, 2H), 0.79 (t,  $J=6.8$  Hz, 2H), 0.53 (t,  $J=6.8$  Hz, 2H). MS  $m/z$  404.2 ( $\text{M}+1$ ) $^+$ .

**[0631]**  $^1\text{H}$  NMR for (F55a) (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  9.85 (d,  $J=6.8$  Hz, 1H), 9.47 (s, 1H), 9.21 (s, 1H), 8.28 (d,  $J=1.6$  Hz, 1H), 8.13 (d,  $J=9.2$  Hz, 1H), 7.94-7.87 (m, 2H), 7.47 (t,  $J=6.8$  Hz, 1H), 7.42 (d,  $J=8.0$  Hz, 1H), 5.04 (m, 1H), 3.26 (t,  $J=7.2$  Hz, 2H), 2.91 (t,  $J=7.2$  Hz, 2H), 2.44 (s, 3H), 1.25 (d,  $J=6.4$  Hz, 6H). MS  $m/z$  434.2 ( $\text{M}+1$ ) $^+$ .

Synthesis of 6-(3,5-dimethyl-1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F106)

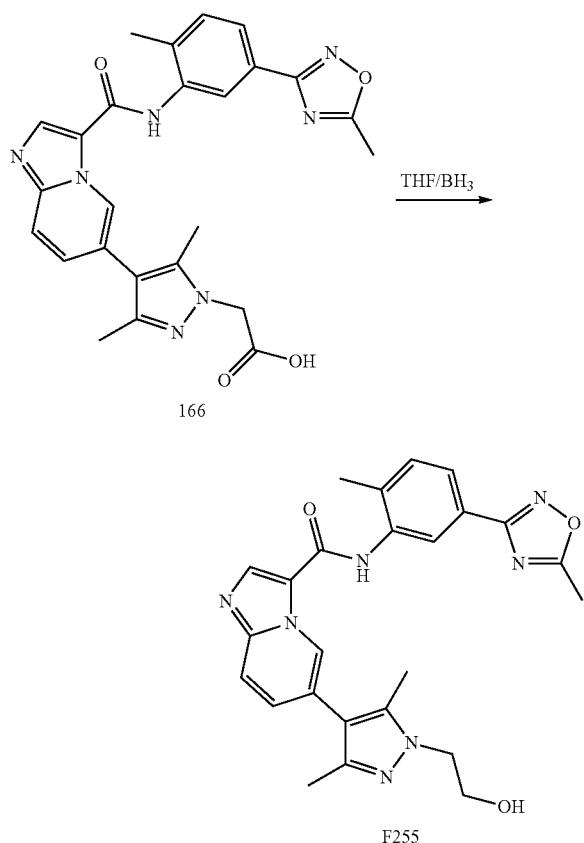
**[0632]**



**[0633]** A mixture of 6-bromo-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (42) (100 mg, 0.243 mmol), 4-(2-(3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)ethyl)morpholine (89 mg, 0.267 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (18 mg, 0.024 mmol) and a solution of 2M sodium carbonate (300  $\mu$ L) in dioxane (1.5 mL) was heated in the microwave at 135°C for 20 minutes. The solvent was reduced under vacuo. The crude product was purified by reverse phase preparative HPLC to obtain 6-(3,5-dimethyl-1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F106) as a tan solid. MS  $m/z$  540.26 (M+1)<sup>+</sup>.

Synthesis of 6-(1-(2-hydroxyethyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F255)

**[0634]**

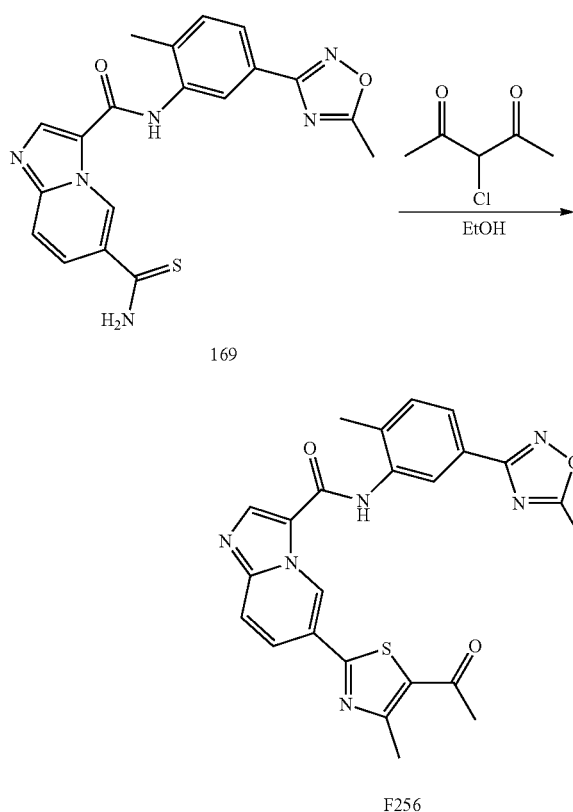


**[0635]** To a stirring suspension of 2-(3,5-dimethyl-4-(3-((2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)-1H-pyrazol-1-yl)acetic acid (166) (25 mg, 0.043 mmol) in anhydrous THF at 0°C was added 1M borane in THF (130  $\mu$ L, 0.129 mmol). The reaction was stirred to room temperature for 20 minutes. The solvent was concentrated and the crude product was purified by reverse phase preparative HPLC to obtain 6-(1-(2-hy-

droxyethyl)-3,5-dimethyl-1H-pyrazol-4-yl)-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (255) as a white solid. <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO)  $\delta$  10.10 (s, 1H), 9.36 (s, 1H), 8.65 (s, 1H), 8.04 (s, 1H), 7.86 (d, J=9.3 Hz, 1H), 7.80 (d, J=7.9 Hz, 1H), 7.55 (d, J=9.3 Hz, 1H), 7.49 (d, J=8.1 Hz, 1H), 4.06 (t, J=5.6 Hz, 2H), 3.71 (t, J=5.6 Hz, 2H), 2.66 (s, 3H), 2.35 (s, 3H), 2.28 (s, 3H), 2.17 (s, 3H). MS  $m/z$  471.20 (M+1)<sup>+</sup>.

Synthesis of 6-(5-acetyl-4-methylthiazol-2-yl)-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F256)

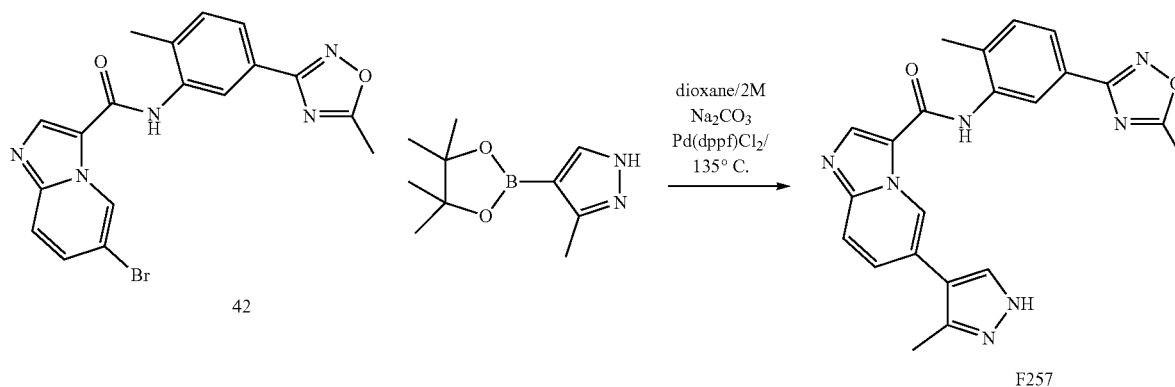
**[0636]**



**[0637]** A stirring suspension of 6-carbamothioyl-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (169) (25 mg, 0.064 mmol) and 3-Chloro-2,4-pentanedione (9  $\mu$ L, 0.076 mmol) in ethanol (1 mL) was refluxed overnight. The solvent was concentrated and the crude product was purified by silica chromatography to obtain 6-(5-acetyl-4-methylthiazol-2-yl)-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F256) as a tan solid. <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) 10.21 (m, 1H), 10.17 (s, 1H), 8.67 (s, 1H), 8.10 (d, J=1.7 Hz, 1H), 8.02 (dd, J=1.9, 9.4 Hz, 1H), 7.92 (dd, J=0.9, 9.4 Hz, 1H), 7.82 (dd, J=1.8, 7.9 Hz, 1H), 7.51 (d, J=8.1 Hz, 1H), 2.73 (s, 3H), 2.67 (s, 3H), 2.60 (s, 3H), 2.38 (s, 3H). MS  $m/z$  472.13 (M+1)<sup>+</sup>.

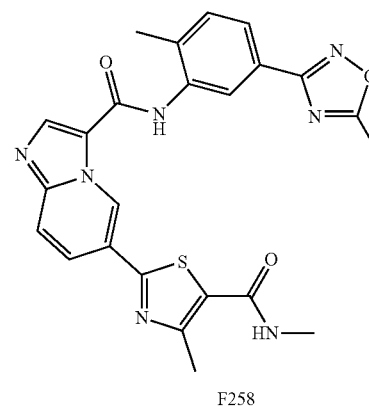
Synthesis of 6-(3-methyl-1H-pyrazol-4-yl)-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F257)

[0638]



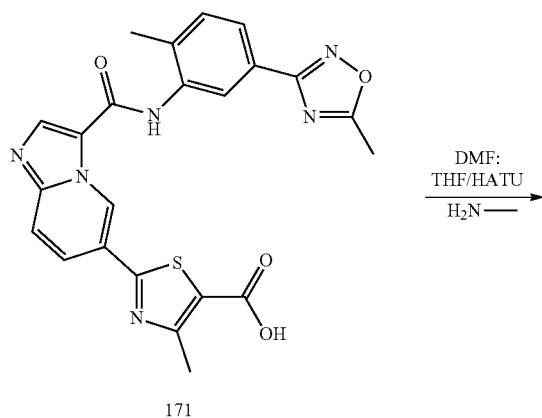
[0639] A mixture of 6-bromo-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (42) (50 mg, 0.121 mmol), 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (30 mg, 0.146 mmol), [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II) (9 mg, 0.024 mmol) and a solution of 2M sodium carbonate (150  $\mu$ L) in anhydrous dioxane (1 mL) was heated in the microwave at 135° C. for 20 minutes. The crude product was purified by reverse phase preparative HPLC to obtain 6-(3-methyl-1H-pyrazol-4-yl)-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F257) as a white solid. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO)  $\delta$  10.14 (s, 1H), 9.59 (s, 1H), 8.66 (s, 1H), 8.04 (d, J=1.7 Hz, 1H), 7.96 (s, 1H), 7.89 (d, J=9.3 Hz, 1H), 7.82 (dd, J=1.8, 8.0 Hz, 2H), 7.50 (d, J=8.1 Hz, 1H), 2.66 (s, 3H), 2.40 (s, 3H), 2.36 (s, 3H), 2.07 (s, 1H). MS *m/z* 413.16 (M+1)<sup>+</sup>.

-continued



Synthesis of N,4-dimethyl-2-(3-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-ylthiazole-5-carboxamide (F258)

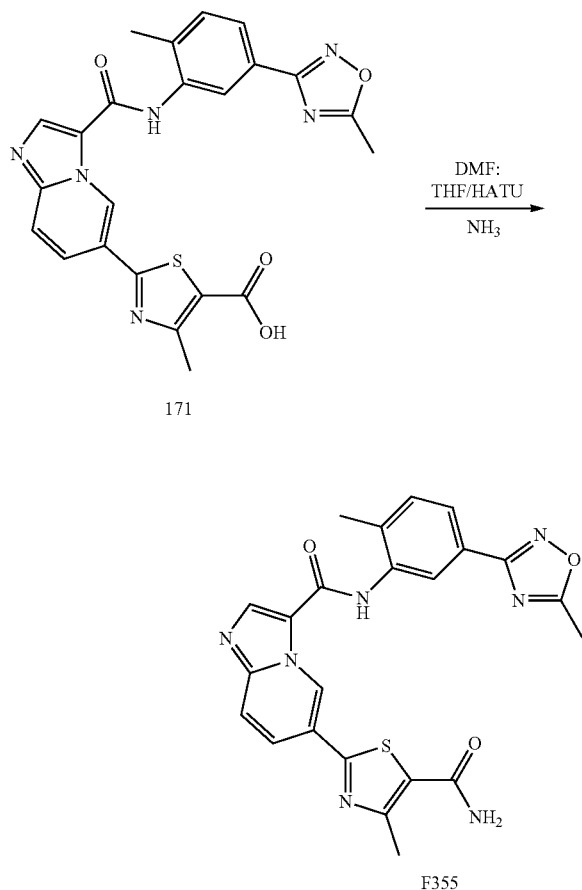
[0640]



[0641] To a stirring suspension of 4-methyl-2-(3-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-ylthiazole-5-carboxylic acid (171) (25 mg, 0.053 mmol) in DMF:THF (1:1, 2 mL) was added HATU (24 mg, 0.063 mmol) and DIPEA (18  $\mu$ L, 0.105 mmol). The reaction mixture was stirred at room temperature for 10 minutes. Then, 2M methylamine in THF (0.3 mL, 0.527 mmol) was added. The reaction was stirred for 3 h. The crude product was purified by reverse phase preparative HPLC to obtain N,4-dimethyl-2-(3-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-ylthiazole-5-carboxamide (F258) as a white solid. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO)  $\delta$  10.16 (s, 1H), 10.15-10.14 (m, 1H), 8.68 (s, 1H), 8.27 (d, J=4.6 Hz, 1H), 8.12 (d, J=1.7 Hz, 1H), 7.99 (dd, J=1.9, 9.4 Hz, 1H), 7.92 (dd, J=0.9, 9.4 Hz, 1H), 7.82 (dd, J=1.8, 7.9 Hz, 1H), 7.51 (d, J=8.1 Hz, 1H), 2.76 (d, J=4.5 Hz, 3H), 2.67 (s, 3H), 2.63 (s, 3H), 2.39 (s, 3H). MS *m/z* 487.14 (M+1)<sup>+</sup>.

Synthesis of 4-methyl-2-(3-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-5-carboxamide (F259)

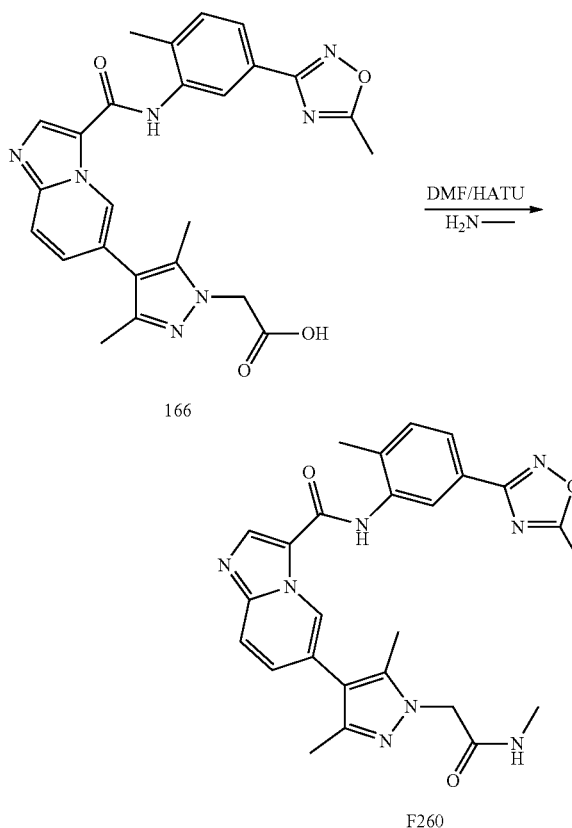
[0642]



[0643] To a stirring suspension of 4-methyl-2-(3-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-5-carboxylic acid (171) (25 mg, 0.053 mmol) in DMF:THF (1:1, 2 mL) was added HATU (24 mg, 0.063 mmol) and DIPEA (18  $\mu$ L, 0.105 mmol). The reaction mixture was stirred at room temperature for 10 minutes. Then, ammonium carbonate (51 mg, 0.527 mmol) was added. The reaction was stirred for 3 h. The crude product was purified by reverse phase preparative HPLC to obtain 4-methyl-2-(3-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-5-carboxamide (F259) as a tan solid.  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO)  $\delta$  10.16 (s, 1H), 10.15-10.14 (m, 1H), 8.67 (s, 1H), 8.11 (s, 1H), 7.98 (dd,  $J=1.9, 9.4$  Hz, 1H), 7.92 (d,  $J=9.4$  Hz, 1H), 7.84-7.80 (m, 1H), 7.79-7.58 (m, 2H), 7.51 (d,  $J=8.1$  Hz, 1H), 2.67 (s, 3H), 2.64 (s, 3H), 2.38 (s, 3H). MS  $m/z$  473.13 (M+1) $^+$ .

Synthesis of 6-(3,5-dimethyl-1-(2-(methylamino)-2-oxoethyl)-1H-pyrazol-4-yl)-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F260)

[0644]

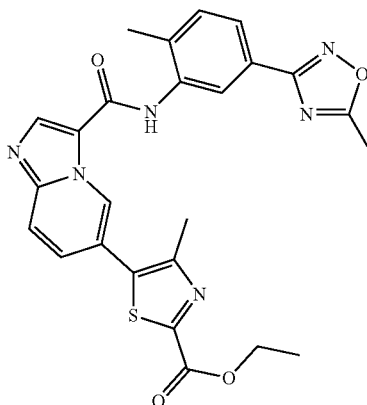
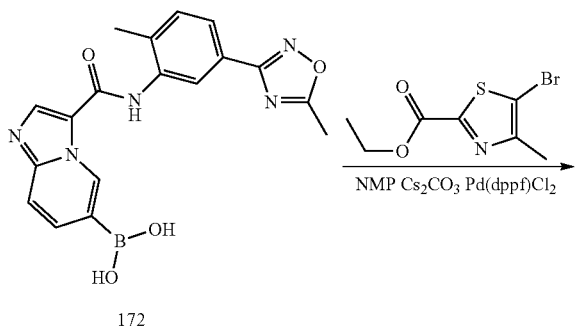


[0645] To a stirring solution of 2-(3,5-dimethyl-4-(3-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)-1H-pyrazol-1-yl)acetic acid (166) (25 mg, 0.043 mmol) in anhydrous N,N-dimethylformamide (1 mL) was added N,N-diisopropylethylamine (15  $\mu$ L, 0.086 mmol) and HATU (20 mg, 0.052 mmol). The reaction mixture was stirred at room temperature for 5 minutes. Next, 2M methylamine in THF (200  $\mu$ L, 0.429 mmol) was added. The reaction was stirred for 15 minutes. The crude product was purified by reverse phase preparative HPLC to obtain 6-(3,5-dimethyl-1-(2-(methylamino)-2-oxoethyl)-1H-pyrazol-4-yl)-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F260) as a white solid.  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO)  $\delta$  10.13 (s, 1H), 9.39 (s, 1H), 8.67 (s, 1H), 8.04 (s, 1H), 8.01 (d,  $J=4.8$  Hz, 1H), 7.89 (d,  $J=9.3$  Hz, 1H), 7.81 (d,  $J=7.9$  Hz, 1H), 7.59 (d,  $J=9.3$  Hz, 1H), 7.49 (d,  $J=8.1$  Hz, 1H), 4.71 (s, 2H), 2.66 (d,  $J=2.3$  Hz, 3H), 2.62 (d,  $J=4.6$  Hz, 3H), 2.36 (s, 3H), 2.23 (s, 3H), 2.17 (s, 3H). MS  $m/z$  498.21 (M+1) $^+$ .



Synthesis of ethyl 4-methyl-5-(3-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-2-carboxylate (F261)

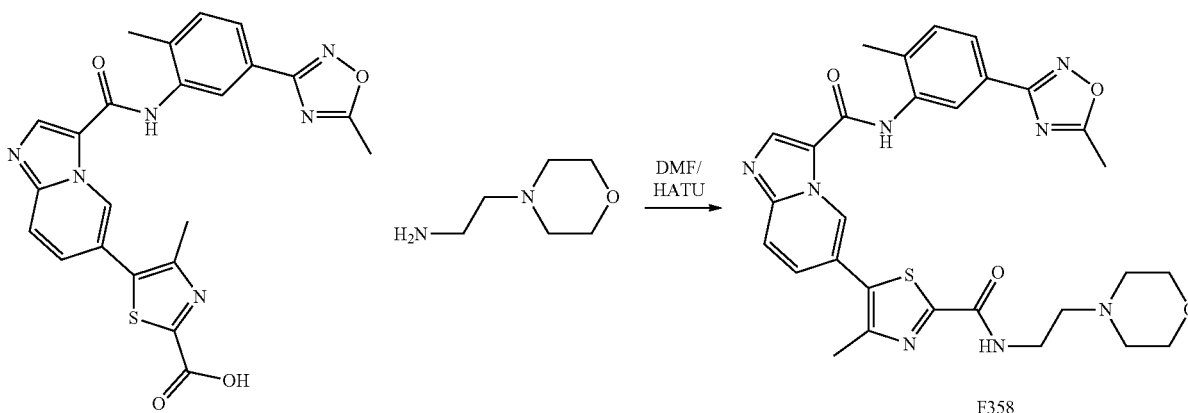
[0646]



[0647] A mixture of (3-((2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)boronic acid (172) (300 mg, 0.795 mmol), ethyl 5-bromo-4-methylthiazole-2-carboxylate (199 mg, 0.795 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (58 mg, 0.080 mmol) and cesium carbonate (311 mg, 0.955 mmol) in anhydrous NMP (2.5 mL) was heated in the microwave at 130° C. for 20 minutes. The crude product was taken in ethyl acetate and water. The organic layer was washed with 2× water/brine mixture and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography to obtain ethyl 4-methyl-5-(3-((2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-2-carboxylate (F261) as a tan solid. <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.17 (s, 1H), 9.71-9.69 (m, 1H), 8.68 (s, 1H), 8.06 (d, J=1.7 Hz, 1H), 7.94 (dd, J=0.9, 9.3Hz, 1H), 7.81 (dd, J=1.8, 7.9 Hz, 1H), 7.75 (dd, J=1.9, 9.3Hz, 1H), 7.50 (d, J=8.0 Hz, 1H), 4.38 (t, J=7.1 Hz, 2H), 2.66 (s, 3H), 2.55 (s, 3H), 2.36 (s, 3H), 1.34 (t, J=7.1 Hz, 3H). MS m/z 502.14 (M+1)<sup>+</sup>.

Synthesis of 4-methyl-5-(3-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)-N-(2-morpholinoethyl)thiazole-2-carboxamide (F262)

[0648]

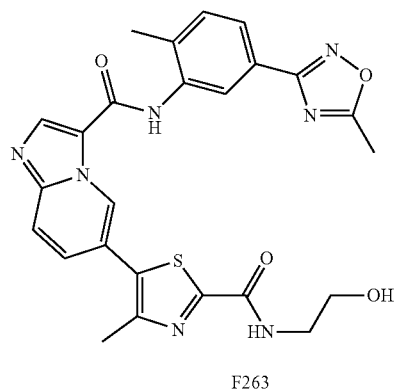
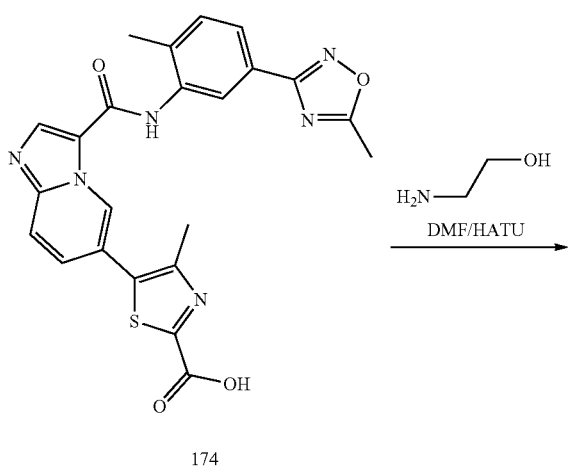


174

**[0649]** To a stirring suspension of 4-methyl-5-(3-((2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-2-carboxylic acid (174) (20 mg, 0.042 mmol) in DMF (1 mL) was added HATU (24 mg, 0.063 mmol) and DIPEA (15  $\mu$ L, 0.084 mmol). The reaction mixture was stirred at room temperature for 10 minutes. Then, 2-morpholinoethanamine (16 mg, 0.126 mmol) was added. The reaction was stirred for 1 h. The crude product was purified by reverse phase preparative HPLC to obtain 4-methyl-5-(3-((2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)-N-(2-morpholinoethyl)thiazole-2-carboxamide (F262) as a tan solid.  $^1\text{H NMR}$  (400 MHz,  $d_6$ -DMSO)  $\delta$  10.17 (s, 1H), 9.68-9.67 (m, 1H), 9.15 (s, 1H), 8.68 (s, 1H), 8.04 (d,  $J=1.7$  Hz, 1H), 7.94 (d,  $J=9.3$  Hz, 1H), 7.83-7.80 (m, 1H), 7.73-7.69 (m, 1H), 7.50 (d,  $J=8.1$  Hz, 1H), 3.98 (s, 2H), 3.65 (s, 4H), 3.55 (s, 2H), 3.35 (s, 2H), 3.16-3.05 (m, 2H), 2.66 (s, 3H), 2.55 (s, 3H), 2.36 (s, 3H). MS  $m/z$  586.21 (M+1) $^+$ .

Synthesis of N-(2-hydroxyethyl)-4-methyl-5-(3(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-2-carboxamide (F263)

**[0650]**

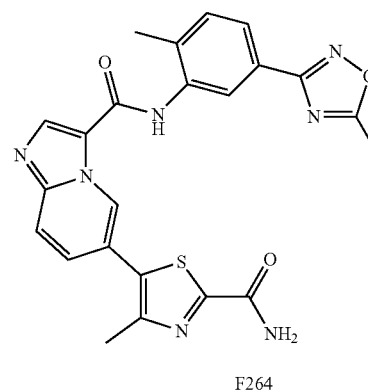
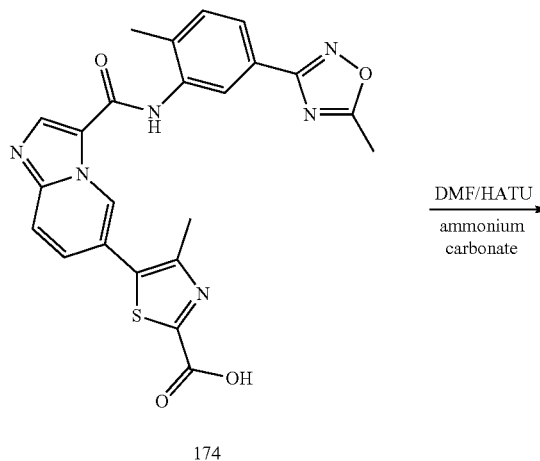


**[0651]** To a stirring suspension of 4-methyl-5-(3-((2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)

imidazo[1,2-a]pyridin-6-yl)thiazole-2-carboxylic acid (174) (20 mg, 0.042 mmol) in DMF (1 mL) was added HATU (24 mg, 0.063 mmol) and DIPEA (15  $\mu$ L, 0.084 mmol). The reaction mixture was stirred at room temperature for 10 minutes. Then, 2-aminoethanol (8 mg, 0.126 mmol) was added. The reaction was stirred for 1 h. The crude product was purified by reverse phase preparative HPLC to obtain N-(2-hydroxyethyl)-4-methyl-5-(3-((2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-2-carboxamide (F263) as a tan solid.  $^1\text{H NMR}$  (400 MHz,  $d_6$ -DMSO)  $\delta$  10.17 (s, 1H), 9.68-9.66 (m, 1H), 8.69 (d,  $J=7.9$  Hz, 2H), 8.05 (d,  $J=1.7$  Hz, 1H), 7.95-7.91 (m, 1H), 7.81 (dd,  $J=1.7, 7.9$  Hz, 1H), 7.72 (dd,  $J=1.9, 9.3$  Hz, 1H), 7.50 (d,  $J=8.1$  Hz, 1H), 3.52 (t,  $J=6.2$  Hz, 2H), 3.35 (t,  $J=6.0$  Hz, 2H), 2.66 (s, 3H), 2.54 (s, 3H), 2.36 (s, 3H). MS  $m/z$  517.15 (M+1) $^+$ .

Synthesis of 4-methyl-5-(3(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-2-carboxamide (F264)

**[0652]**

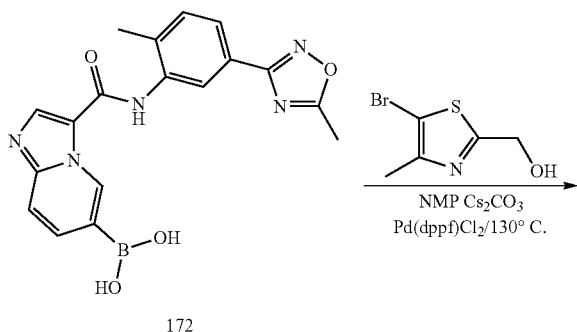


**[0653]** To a stirring suspension of 4-methyl-5-(3-((2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-2-carboxylic acid (174)

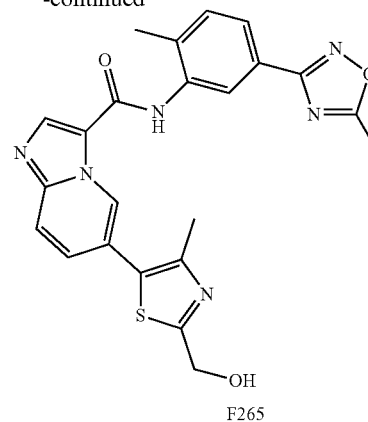
(20 mg, 0.042 mmol) in DMF (1 mL) was added HATU (24 mg, 0.063 mmol) and DIPEA (15  $\mu$ L, 0.084 mmol). The reaction mixture was stirred at room temperature for 10 minutes. Then, ammonium carbonate (16 mg, 0.169 mmol) was added. The reaction was stirred for 1 h. The crude product was purified by reverse phase preparative HPLC to obtain 4-methyl-5-(3-((2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)thiazole-2-carboxamide (F264) as a white solid.  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO)  $\delta$  10.16 (s, 1H), 9.67-9.66 (m, 1H), 8.67 (s, 1H), 8.22 (s, 1H), 8.05 (s, 1H), 7.92 (d,  $J=9.3\text{Hz}$ , 1H), 7.88 (s, 1H), 7.81 (d,  $J=7.9\text{Hz}$ , 1H), 7.71 (d,  $J=11.2\text{Hz}$ , 1H), 7.50 (d,  $J=8.1\text{Hz}$ , 1H), 2.66 (s, 3H), 2.52 (d,  $J=5.1\text{Hz}$ , 3H), 2.36 (s, 3H). MS  $m/z$  473.13 ( $M+1$ ) $^+$ .

Synthesis of 6-(2-(hydroxymethyl)-4-methylthiazol-5-yl)-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F265)

[0654]



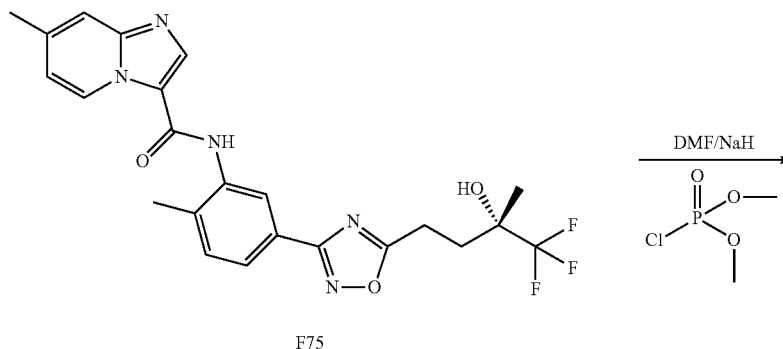
-continued

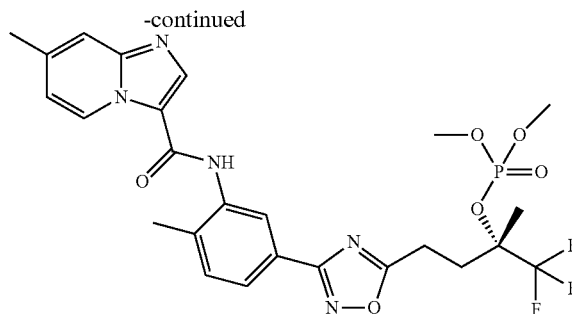


[0655] A mixture of 3-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenylcarbamoyl)imidazo[1,2-a]pyridin-6-ylboronic acid (172) (20 mg, 0.053 mmol), (5-bromo-4-methylthiazol-2-yl)methanol (11 mg, 0.053 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (4 mg, 0.005 mmol) and cesium carbonate (21 mg, 0.064 mmol) in anhydrous NMP (1 mL) was heated in the microwave at 130 $^{\circ}$  C. for 20 minutes. The crude product was filtered through celite and purified by reverse phase preparative HPLC to obtain 6-(2-(hydroxymethyl)-4-methylthiazol-5-yl)-N-(2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F265) as a tan solid.  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO)  $\delta$  10.13 (d, 1H), 9.60-9.59 (m, 1H), 8.65 (s, 1H), 8.05 (s, 1H), 7.89 (d,  $J=9.3\text{Hz}$ , 1H), 7.84-7.78 (m, 1H), 7.65 (dd,  $J=1.9, 9.3\text{Hz}$ , 1H), 7.49 (d,  $J=8.1\text{Hz}$ , 1H), 4.71 (s, 2H), 2.66 (s, 3H), 2.43 (s, 3H), 2.36 (s, 3H). MS  $m/z$  460.13 ( $M+1$ ) $^+$ .

Synthesis of (S)-dimethyl (1,1,1-trifluoro-2-methyl-4-(3-(4-methyl-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)butan-2-yl) phosphate (F267)

[0656]





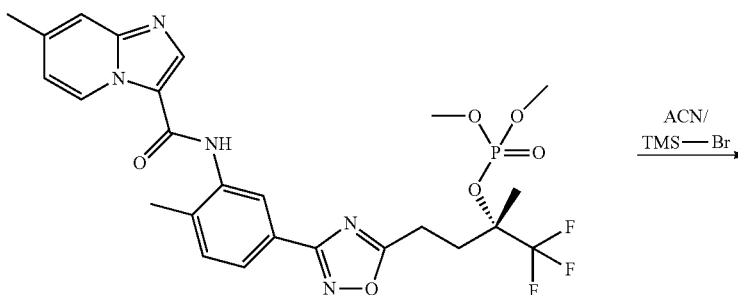
F267

**[0657]** To a stirring solution of (S)-7-methyl-N-(2-methyl-5-(5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F75) (50 mg, 0.106 mmol) in anhydrous DMF (1 mL) at 0° C. was added sodium hydride (60%, 42 mg, 1.06 mmol). The reaction was stirred to room temperature under argon for 20 minutes. The reaction mixture was cooled back to 0° C. and dimethyl phosphorochloridate (76 mg, 0.528 mmol) dissolved in anhydrous DMF (0.5 mL) was added. The reaction was stirred at room temperature under Argon overnight. The crude product was purified by reverse phase preparative HPLC to obtain (S)-dimethyl (1,1,1-trifluoro-2-methyl-4-(3-(4-methyl-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)butan-2-yl) phosphate (F267) as a white solid.

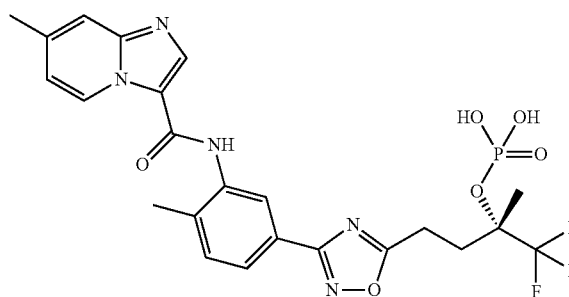
**[0658]** <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO) δ 10.12 (s, 1H), 9.38 (d, J=7.1 Hz, 1H), 8.64 (s, 1H), 8.07 (s, 1H), 7.83 (d, J=7.9 Hz, 1H), 7.67 (s, 1H), 7.50 (d, J=8.2 Hz, 1H), 7.19 (s, 1H), 3.72 (d, J=4.2 Hz, 3H), 3.69 (d, J=4.2 Hz, 3H), 3.36-3.31 (m, 1H), 3.23 (s, 2H), 2.48 (s, 3H), 2.36 (s, 3H), 1.73 (s, 3H), 1.50 (s, 1H). MS m/z 581.17 (M+1)<sup>+</sup>.

Synthesis of (S)-1,1,1-trifluoro-2-methyl-4-(3-(4-methyl-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)butan-2-yl dihydrogen phosphate (F268)

**[0659]**



F267



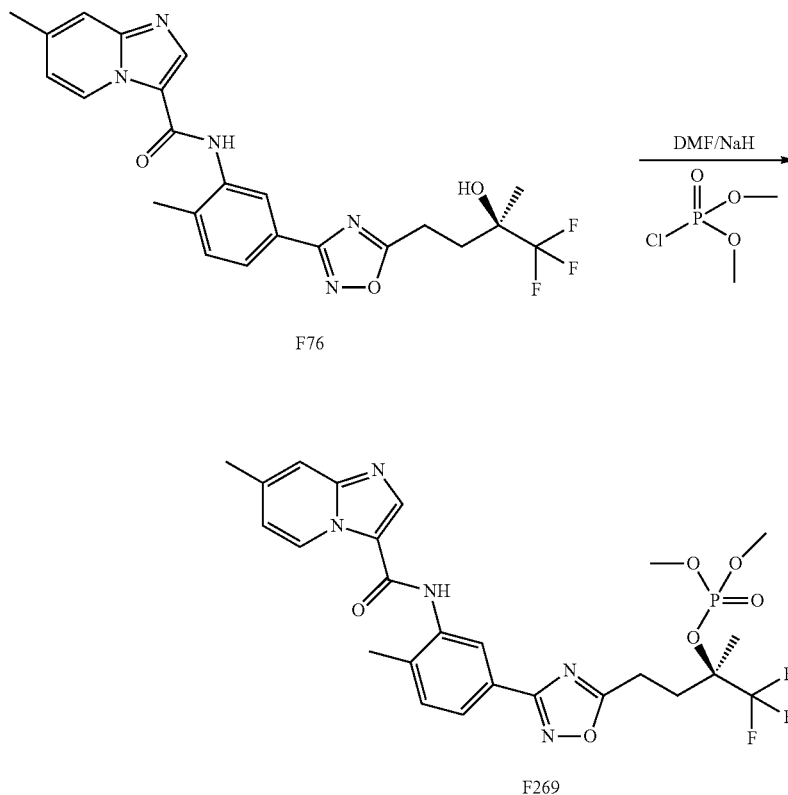
F268

**[0660]** To a stirring solution of (S)-dimethyl 1,1,1-trifluoro-2-methyl-4-(3-(4-methyl-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)butan-2-yl phosphate (F267) (80 mg, 0.138 mmol) in anhydrous acetonitrile (1 mL) at 0° C. was added bromotrimethylsilane (55  $\mu$ L, 0.413 mmol). The reaction was stirred to room temperature for 1 h (another 3 eq of bromotrimethylsilane was added to get the reaction to go to completion). The reaction was cooled back to 0° C. and quenched with a saturated solution of sodium bicarbonate. The crude product was purified by reverse phase preparative HPLC to obtain (S)-1,1,1-trifluoro-2-methyl-4-(3-(4-methyl-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)butan-2-yl dihydrogen phosphate (F268) as a white solid.  $^1\text{H NMR}$  (400 MHz,  $d_6$ -DMSO)  $\delta$  10.14 (s, 1H), 9.40 (d,  $J=7.2$  Hz, 1H), 8.66 (s, 1H), 8.07 (s, 1H), 7.83 (d,  $J=7.9$  Hz, 1H), 7.69 (s, 1H), 7.50 (d,  $J=8.2$  Hz, 1H), 7.21 (s, 1H), 3.23 (d,  $J=5.0$  Hz, 2H), 2.49 (m, 3H), 2.47-2.42 (m, 2H), 2.36 (s, 3H), 1.70 (s, 3H). MS  $m/z$  553.13 ( $M+1$ ) $^+$ .

Synthesis of (R)-dimethyl (1,1,1-trifluoro-2-methyl-4-(3-(4-methyl-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)butan-2-yl) phosphate (F269)

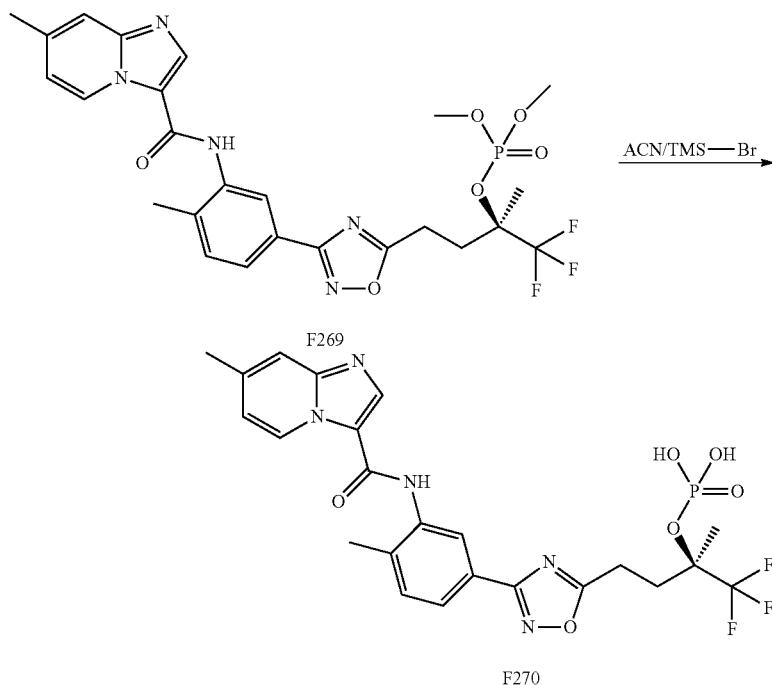
**[0661]**

**[0662]** To a stirring solution of (R)-7-methyl-N-(2-methyl-5-(5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F76) (50 mg, 0.106 mmol) in anhydrous DMF (1 mL) at 0° C. was added sodium hydride (60%, 42 mg, 1.06 mmol). The reaction was stirred to room temperature under argon for 20 minutes. The reaction mixture was cooled back to 0° C. and dimethyl phosphorochloridate (23  $\mu$ L, 0.211 mmol) was added drop-wise. More dimethyl phosphorochloridate was added as needed to let the reaction go to completion (20-30 minutes). The reaction was carried out in three batches. The combined crude product was purified by reverse phase preparative HPLC to obtain (R)-dimethyl (1,1,1-trifluoro-2-methyl-4-(3-(4-methyl-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)butan-2-yl) phosphate (F269) as a white solid.  $^1\text{H NMR}$  (400 MHz,  $d_6$ -DMSO)  $\delta$  10.20 (s, 1H), 9.42 (d,  $J=7.1$  Hz, 1H), 8.70 (s, 1H), 8.07 (d,  $J=1.6$  Hz, 1H), 7.84 (dd,  $J=1.8, 7.9$  Hz, 1H), 7.73 (s, 1H), 7.51 (d,  $J=8.2$  Hz, 1H), 7.25 (d,  $J=7.1$  Hz, 1H), 3.72 (d,  $J=4.0$  Hz, 3H), 3.69 (d,  $J=4.0$  Hz, 3H), 3.23 (t,  $J=7.0$  Hz, 2H), 2.60-2.54 (m, 2H), 2.49 (s, 3H), 2.36 (s, 3H), 1.73 (s, 3H). MS  $m/z$  581.17 ( $M+1$ ) $^+$ .



Synthesis of (R)-1,1,1-trifluoro-2-methyl-4-(3-(4-methyl-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)butan-2-yl dihydrogen phosphate (F270)

[0663]

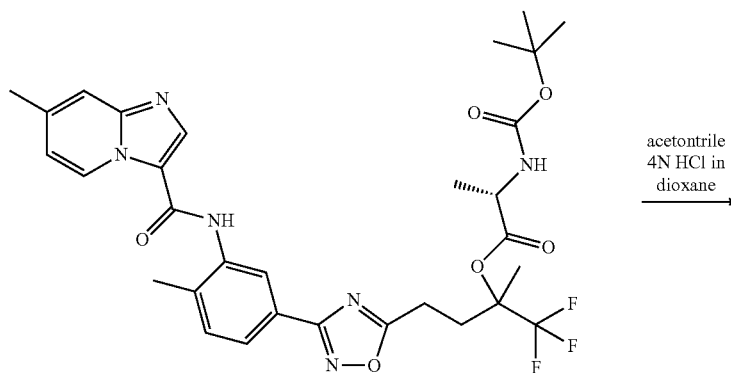


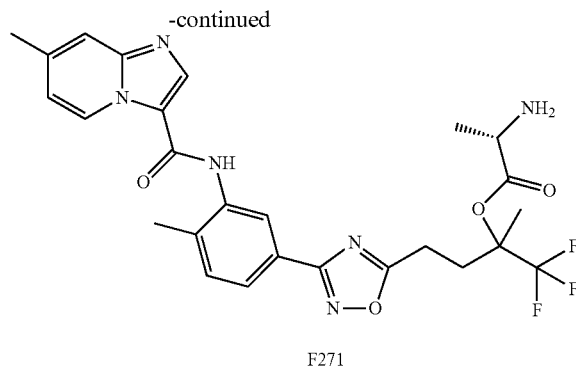
[0664] To a stirring solution of (R)-dimethyl 1,1,1-trifluoro-2-methyl-4-(3-(4-methyl-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)butan-2-yl phosphate (F269) (75 mg, 0.129 mmol) in anhydrous acetonitrile (1 mL) at 0° C. was added bromotrimethylsilane (68  $\mu$ L, 0.516 mmol). The reaction was stirred to room temperature for 3 h (another 3 eq of bromotrimethylsilane was added to get the reaction to go to completion). The reaction was cooled back to 0° C. and quenched with a saturated solution of sodium bicarbonate. The crude product was purified by reverse phase preparative HPLC to obtain (R)-1,1,1-trifluoro-2-methyl-4-(3-(4-methyl-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)

butan-2-yl dihydrogen phosphate (F270) as a white solid. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO)  $\delta$  10.02 (s, 1H), 9.31 (d, *J*=7.2 Hz, 1H), 8.54 (s, 1H), 8.01 (d, *J*=1.7 Hz, 1H), 7.76 (dd, *J*=1.7, 7.9 Hz, 1H), 7.59 (s, 1H), 7.43 (d, *J*=8.2 Hz, 1H), 7.08 (d, *J*=7.2 Hz, 1H), 3.16 (dd, *J*=4.9, 9.9 Hz, 2H), 2.49 (s, 3H), 2.47-2.44 (m, 2H), 2.30 (s, 3H), 1.63 (s, 3H). MS *m/z* 553.13 (*M*+1)<sup>+</sup>.

Synthesis of (2S)-1,1,1-trifluoro-2-methyl-4-(3-(4-methyl-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)butan-2-yl 2-aminopropanoate (F271)

[0665]





**[0666]** To a stirring solution of (2S)-1,1,1-trifluoro-2-methyl-4-(3-(4-methyl-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)butan-2-yl 2-((tert-butoxycarbonyl)amino)propanoate (prepared in a similar manner as F267 and F269 starting from F67 and (S)-2,5-dioxopyrrolidin-1-yl 2-((tert-butoxycarbonyl)amino)propanoate) (25 mg, 0.039 mmol) in acetonitrile (1 mL) was added 4N HCl in dioxane (1 mL). The reaction was stirred at room temperature for 45 minutes. The product was purified by reverse phase preparative HPLC to obtain (2S)-1,1,1-trifluoro-2-methyl-4-(3-(4-methyl-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-

yl)butan-2-yl 2-aminopropanoate (F271) as a white solid.  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO)  $\delta$  10.06 (s, 1H), 9.35 (d,  $J=7.1$  Hz, 1H), 8.61 (s, 1H), 8.31 (s, 2H), 8.07 (s, 1H), 7.82 (dd,  $J=1.7, 7.9$  Hz, 1H), 7.65 (s, 1H), 7.50 (d,  $J=8.2$  Hz, 1H), 7.13 (d,  $J=7.1$  Hz, 1H), 4.27-4.21 (m, 1H), 3.21 (s, 2H), 2.72-2.66 (m, 2H), 2.46 (s, 3H), 2.36 (s, 3H), 1.78 (d,  $J=5.5$  Hz, 3H), 1.42 (dd,  $J=7.2, 9.5$  Hz, 3H). MS  $m/z$  544.20 ( $M+1$ ) $^+$ .

**[0667]** Representative compounds of Formula (I) and Formula (II) with  $\text{IC}_{50}$  values in the range of 1 nM to 100 nM, and prepared following the procedures described above, are set forth in Table 1.

TABLE 1

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F1		$^1\text{H}$ NMR (400 MHz, $d_6$ -DMSO) $\delta$ 10.22 (s, 1H), 9.55-9.51 (m, 1H), 8.72 (s, 1H), 8.44 (d, 1.6 Hz, 1H), 7.91-7.88 (m, 1H), 7.85 (dd, $J=1.6, 7.6$ Hz, 1H), 7.73-7.69 (m, 1H), 7.53 (d, $J=8.0$ Hz, 1H), 7.35-7.31 (m, 1H), 3.42 (t, $J=7.2$ Hz, 2H), 3.08 (t, $J=7.2$ Hz, 2H), 2.37 (s, 3H). MS $m/z$ 373.3 ( $M+1$ ) $^+$ .	0.078
F2		$^1\text{H}$ NMR (400 MHz, $d_6$ -DMSO) $\delta$ 10.14 (s, 1H), 9.52-9.49 (m, 1H), 8.68 (s, 1H), 8.08 (d, $J=1.6$ Hz, 1H), 7.88-7.85 (m, 1H), 7.82 (dd, $J=1.6, 7.6$ Hz, 1H), 7.67-7.63 (m, 1H), 7.50 (d, $J=8.0$ Hz, 1H), 7.30-7.27 (m, 1H), 7.11-7.08 (m, 1H), 3.39 (q, $J=6.4$ Hz, 2H), 3.10 (t, $J=6.4$ Hz, 2H), 2.37 (s, 3H), 1.33 (s, 9H). MS $m/z$ 463.5 ( $M+1$ ) $^+$ .	0.063
F3		$^1\text{H}$ NMR (400 MHz, $d_6$ -DMSO) $\delta$ 10.19 (s, 1H), 9.53-9.51 (m, 1H), 8.71 (s, 1H), 8.06 (d, $J=1.6$ Hz, 1H), 7.91-7.87 (m, 1H), 7.83 (dd, $J=1.6, 8.0$ Hz, 1H), 7.72-7.68 (m, 1H), 7.50 (d, $J=8.0$ Hz, 1H), 7.34-7.31 (m, 1H), 3.42 (t, $J=6.0$ Hz, 2H), 3.23 (s, 3H), 3.03 (t, $J=7.2$ Hz, 2H), 2.37 (s, 3H), 2.06-1.99 (m, 2H). MS $m/z$ 392.4 ( $M+1$ ) $^+$ .	0.044

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F4		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.23 (s, 1H), 9.54 (d, $J = 7.2$ Hz, 1H), 8.48 (s, 1H), 8.06 (s, 1H), 7.92 (d, $J = 8.8$ Hz, 1H), 7.82 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.72-7.76 (m, 1H), 7.50 (d, $J = 8$ Hz, 1H), 7.29 (td, $J = 6.8, 1.2$ Hz, 1H), 3.35 (q, $J = 7.2$ Hz, 2H), 3.25 (q, $J = 7.2$ Hz, 2H), 3.17 (t, $J = 7.2$ Hz, 2H), 2.93 (t, $J = 7.2$ Hz, 1H), 2.37 (s, 3H), 1.15 (t, $J = 7.2$ Hz, 3H), 0.99 (t, $J = 7.2$ Hz, 3H). MS $m/z$ 447.5 ( $M + 1$ ) <sup>+</sup> .	0.067
F5		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.17 (s, 1H), 9.51 (d, $J = 6.8$ Hz, 1H), 8.69 (s, 1H), 8.04 (s, 1H), 7.87 (d, $J = 9.2$ Hz, 1H), 7.82 (dd, $J = 7.6, 0.8$ Hz, 1H), 7.67 (t, $J = 8.0$ Hz, 1H), 7.49 (d, $J = 8$ Hz, 1H), 7.30 (t, $J = 6.8$ Hz, 1H), 3.07-3.25 (m, 4H), 2.36 (s, 3H), 2.17 (s, 3H). MS $m/z$ 390.4 ( $M + 1$ ) <sup>+</sup> .	0.032
F6		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.09 (s, 1H), 9.48 (d, $J = 7.2$ Hz, 1H), 8.64 (s, 1H), 8.08 (d, $J = 0.8$ Hz, 1H), 7.78-7.86 (m, 2H), 7.75 (t, $J = 6.0$ Hz, 1H), 7.60 (t, $J = 9.2$ Hz, 1H), 7.50 (d, $J = 8$ Hz, 1H), 7.24 (t, $J = 7.2$ Hz, 1H), 4.50 (d, $J = 5.6$ Hz, 2H), 2.37 (s, 3H), 1.40 (s, 9H). MS $m/z$ 449.4 ( $M + 1$ ) <sup>+</sup> .	0.008
F7		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.15 (s, 1H), 9.50 (d, $J = 7.2$ Hz, 1H), 8.68 (s, 1H), 8.10 (d, $J = 0.8$ Hz, 1H), 7.81-7.88 (m, 2H), 7.66 (t, $J = 8.0$ Hz, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.29 (t, $J = 7.2$ Hz, 1H), 4.38 (s, 2H), 4.17 (q, $J = 7.2$ Hz, 2H), 2.37 (s, 3H), 1.22 (t, $J = 7.2$ Hz, 3H). MS $m/z$ 406.4 ( $M + 1$ ) <sup>+</sup> .	0.087
F8		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.12 (s, 1H), 9.50 (d, $J = 6.8$ Hz, 1H), 8.66 (s, 1H), 8.04 (s, 1H), 8.06 (d, $J = 0.8$ Hz, 1H), 7.80-7.87 (m, 2H), 7.63 (t, $J = 8.0$ Hz, 1H), 7.49 (d, $J = 8$ Hz, 1H), 7.26 (t, $J = 6.8$ Hz, 1H), 3.01-3.35 (m, 2H), 2.36 (s, 3H), 1.85-1.91 (m, 2H), 1.14 (s, 6H). MS $m/z$ 406.4 ( $M + 1$ ) <sup>+</sup> .	0.063
F9		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.15 (s, 1H), 9.51 (d, $J = 6.9$ Hz, 1H), 8.69 (s, 1H), 8.07 (s, 1H), 7.85 (dd, $J = 8.5, 19.0$ Hz, 2H), 7.66 (s, 1H), 7.50 (d, $J = 8.1$ Hz, 1H), 7.29 (s, 1H), 3.60-3.70 (m, 2H), 2.96-3.10 (m, 2H), 2.37 (s, 3H), 1.77-1.98 (m, 2H), 1.11 (d, $J = 6.2$ Hz, 3H). MS $m/z$ 392.4 ( $M + 1$ ) <sup>+</sup> .	0.087



TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F10		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.15 (s, 1H), 9.51 (d, $J = 6.9$ Hz, 1H), 8.68 (s, 1H), 8.08 (s, 1H), 7.65-7.89 (m, 2H), 7.66 (s, 1H), 7.51 (d, $J = 8.1$ Hz, 1H), 7.29 (s, 1H), 3.84 (t, $J = 6.3$ Hz, 2H), 3.48 (q, $J = 7.0$ Hz, 2H), 3.26 (t, $J = 6.3$ Hz, 2H), 2.37 (s, 3H), 1.08 (t, $J = 7.0$ Hz, 3H). MS $m/z$ 392.4 ( $M + 1$ ) $^+$ .	0.042
F11		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.13 (s, 1H), 9.53 (d, $J = 6.9$ Hz, 1H), 8.69 (s, 1H), 8.11 (s, 1H), 7.76-7.91 (m, 2H), 7.69-7.61 (m, 1H), 7.53 (d, $J = 8.1$ Hz, 1H), 7.30 (s, 1H), 2.70 (s, 3H), 2.40 (s, 3H). MS $m/z$ 334.3 ( $M + 1$ ) $^+$ .	0.086
F12		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.14 (s, 1H), 9.50 (d, $J = 6.9$ Hz, 1H), 8.68 (s, 1H), 8.10 (s, 1H), 7.76-7.91 (m, 2H), 7.65 (s, 1H), 7.52 (d, $J = 8.1$ Hz, 1H), 7.28 (s, 1H), 4.86 (s, 2H), 3.64 (q, $J = 7.0$ Hz, 2H), 2.37 (s, 3H), 1.18 (t, $J = 7.0$ Hz, 3H). MS $m/z$ 378.4 ( $M + 1$ ) $^+$ .	0.049
F13		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.12 (s, 1H), 9.52-9.49 (m, 1H), 8.69 (s, 1H), 8.07 (d, $J = 1.6$ Hz, 1H), 7.88-7.84 (m, 1H), 7.83-7.78 (m, 2H), 7.68-7.63 (m, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 7.31-7.27 (m, 1H), 5.01-4.94 (m, 1H), 2.37 (s, 3H), 1.51 (d, $J = 7.2$ Hz, 3H), 1.40 (s, 9H). MS $m/z$ 463.5 ( $M + 1$ ) $^+$ .	0.093
F14		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.18 (s, 1H), 9.52 (d, $J = 6.9$ Hz, 1H), 8.70 (s, 1H), 8.11 (d, $J = 1.7$ Hz, 1H), 7.93-7.83 (m, 2H), 7.74-7.64 (m, 1H), 7.53 (d, $J = 8.1$ Hz, 1H), 7.31 (t, $J = 6.4$ Hz, 1H), 4.86 (q, $J = 6.7$ Hz, 1H), 3.37 (s, 3H), 2.38 (s, 3H), 1.56 (d, $J = 6.7$ Hz, 3H). MS $m/z$ 378.4 ( $M + 1$ ) $^+$ .	0.099
F15		MS $m/z$ 446.1 ( $M + 1$ ) $^+$ .	0.082

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F16		MS m/z 500.1 (M + 1) <sup>+</sup> .	0.022
F17		MS m/z 487.1 (M + 1) <sup>+</sup> .	0.067
F18		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.18 (s, 1H), 9.52-9.50 (m, 1H), 8.70 (s, 1H), 8.18 (d, J = 7.6 Hz, 1H), 8.08 (d, J = 1.6 Hz, 1H), 7.89-7.86 (m, 1H), 7.84 (dd, J = 2.0, 8.0 Hz, 1H), 7.70-7.65 (m, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.32-7.29 (m, 1H), 5.06-4.99 (m, 1H), 3.04 (s, 3H), 2.37 (s, 3H), 1.59 (d, J = 7.2 Hz, 3H). MS m/z 441.5 (M + 1) <sup>+</sup> .	0.098
F19		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.17 (s, 1H), 9.52-9.48 (m, 1H), 8.68 (s, 1H), 8.06 (d, J = 1.6 Hz, 1H), 7.88-7.85 (m, 1H), 7.84-7.81 (m, 1H), 7.67-7.63 (m, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.31-7.26 (m, 1H), 4.78-4.76 (m, 2H), 2.99 (s, 3H), 2.37 (s, 3H), 1.28 (s, 9H). MS m/z 463.5 (M + 1) <sup>+</sup> .	0.057
F20		MS m/z 441.5 (M + 1) <sup>+</sup> .	0.061
F21		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.14 (s, 1H), 9.48 (s, 1H), 8.65 (s, 1H), 8.05 (s, 1H), 7.85 (d, J = 9.2 Hz, 2H), 7.70-7.58 (m, 1H), 7.51 (d, J = 8.1 Hz, 1H) 7.26 (s, 1H), 4.73 (br s, 2H), 3.44-3.30 (m, 2H), 2.36 (s, 3H), 1.41 (s, 4H), 1.25 (s, 5H), 1.12 (t, J = 7.1 Hz, 3H). MS m/z 477.53 (M + 1) <sup>+</sup> .	0.055

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F22		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.19 (s, 1H), 9.51 (d, $J = 7.0$ Hz, 1H), 8.70 (s, 1H), 8.08 (d, $J = 1.7$ Hz, 1H), 7.91-7.83 (m, 2H), 7.71-7.66 (m, 1H), 7.52 (d, $J = 8.1$ Hz, 1H), 7.31 (t, $J = 6.5$ Hz, 1H), 4.85 (s, 2H), 3.37 (q, $J = 7.1$ Hz, 2H), 3.09 (s, 3H), 2.37 (s, 3H), 1.17 (t, $J = 7.1$ Hz, 3H). MS $m/z$ 455.50 ( $M + 1$ ) $^+$ .	0.089
F23		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.20 (s, 1H), 9.51 (d, $J = 6.9$ Hz, 1H), 8.70 (s, 1H), 8.05 (s, 1H), 7.91-7.83 (m, 2H), 7.69 (s, 1H), 7.51 (d, $J = 8.1$ Hz, 1H), 7.31 (s, 1H), 4.82 (s, 2H), 3.51-3.65 (m, 3H), 3.43 (q, $J = 7.1$ Hz, 2H), 2.36 (s, 3H), 1.12 (t, $J = 7.1$ Hz, 3H). MS $m/z$ 435.45 ( $M + 1$ ) $^+$ .	0.059
F24		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.43 (s, 1H), 10.15 (s, 1H), 9.50 (d, $J = 7.0$ Hz, 1H), 8.67 (s, 1H), 8.06 (s, 1H), 7.93-7.79 (m, 2H), 7.64 (s, 1H), 7.52 (d, $J = 8.1$ Hz, 1H), 7.28 (s, 1H), 4.84 (d, $J = 5.6$ Hz, 2H), 2.37 (s, 3H). MS $m/z$ 445.37 ( $M + 1$ ) $^+$ .	0.056
F25		MS $m/z$ 455.50 ( $M + 1$ ) $^+$ .	0.079

TABLE 1-continued

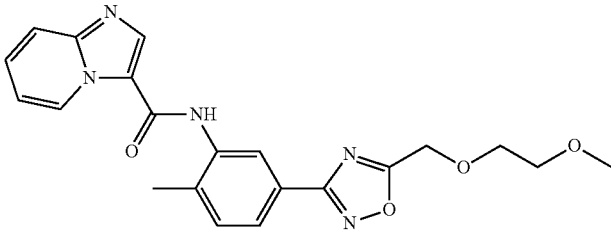
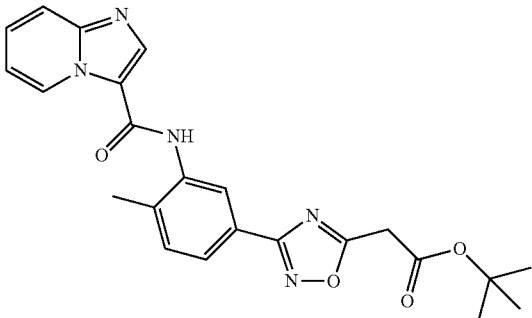
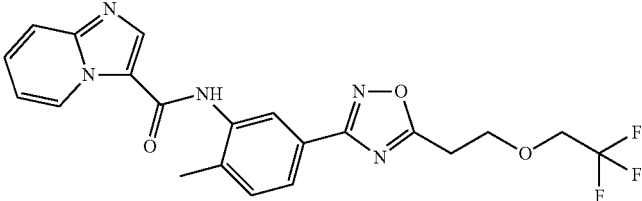
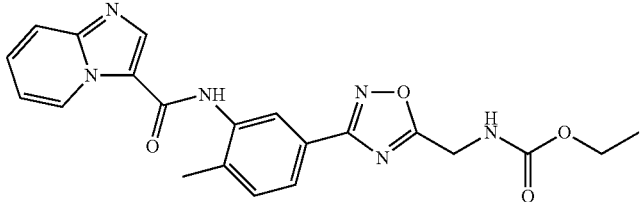
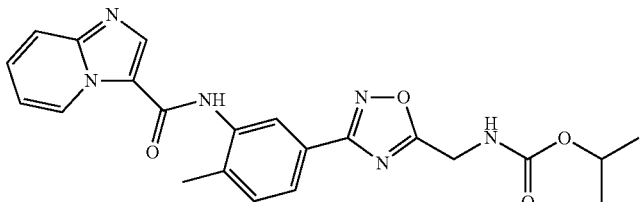
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F26		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ = 10.19 (s, 1H), 9.53 (d, $J$ = 6.9 Hz, 1H), 8.72 (s, 1H), 8.11 (s, 1H), 7.87 (dd, $J$ = 8.5, 18.1 Hz, 2H), 7.70 (s, 1H), 7.53 (d, $J$ = 8.1 Hz, 1H), 7.33 (s, 1H), 4.91 (s, 2H), 3.79-3.67 (m, 2H), 3.57-3.46 (m, 2H), 3.25 (s, 3H), 2.38 (s, 3H). MS $m/z$ 408.0 ( $M + 1$ ) $^+$ .	0.059
F27		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ = 10.18 (s, 1H), 9.53-9.51 (m, 1H), 8.71 (s, 1H), 8.10 (d, $J$ = 1.6 Hz, 1H), 7.90-7.87 (m, 1H), 7.83 (dd, $J$ = 1.6, 8.0 Hz, 1H), 7.71-7.67 (m, 1H), 7.52 (d, $J$ = 8.0 Hz, 1H), 7.34-7.30 (m, 1H), 4.27 (s, 2H), 2.38 (s, 3H), 1.43 (s, 9H). MS $m/z$ 434.18 ( $M + 1$ ) $^+$ .	0.022
F28		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ = 10.16 (s, 1H), 9.51 (d, $J$ = 6.9 Hz, 1H), 8.69 (s, 1H), 8.07 (s, 1H), 7.89-7.80 (m, 2H), 7.66 (s, 1H), 7.51 (d, $J$ = 8.1 Hz, 1H), 7.29 (s, 1H), 4.14 (q, $J$ = 9.4 Hz, 2H), 4.07 (t, $J$ = 6.2 Hz, 2H), 3.34 (t, $J$ = 6.2 Hz, 2H), 2.37 (s, 3H). MS $m/z$ 446.39 ( $M + 1$ ) $^+$ .	0.007
F29		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ = 10.19 (s, 1H), 9.53 (d, $J$ = 7.0 Hz, 1H), 8.72 (s, 1H), 8.08 (d, $J$ = 1.7 Hz, 1H), 8.02 (t, $J$ = 5.9 Hz, 1H), 7.89-7.80 (m, 2H), 7.74-7.68 (m, 1H), 7.51 (d, $J$ = 8.1 Hz, 1H), 7.33 (t, $J$ = 6.9 Hz, 1H), 4.56 (d, $J$ = 5.9 Hz, 2H), 4.03 (q, $J$ = 7.1 Hz, 2H), 2.37 (s, 3H), 1.18 (t, $J$ = 7.1 Hz, 3H). MS $m/z$ 421.42 ( $M + 1$ ) $^+$ .	0.08
F30		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ = 10.19 (s, 1H), 9.53 (d, $J$ = 7.0 Hz, 1H), 8.72 (s, 1H), 8.08 (d, $J$ = 1.7 Hz, 1H), 8.02 (t, $J$ = 5.9 Hz, 1H), 7.89-7.80 (m, 2H), 7.74-7.68 (m, 1H), 7.51 (d, $J$ = 8.1 Hz, 1H), 7.33 (t, $J$ = 6.9 Hz, 1H), 4.82-4.74 (m, 1H), 4.55 (d, $J$ = 6.2 Hz, 2H), 2.37 (s, 3H), 1.19 (d, $J$ = 6.2 Hz, 6H). MS $m/z$ 435.42 ( $M + 1$ ) $^+$ .	0.061

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F31		MS m/z 432.1 (M + 1) <sup>+</sup> .	0.058
F32		MS m/z 422.1 (M + 1) <sup>+</sup> .	0.072
F33		<sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) $\delta$ 9.47 (m, 1H), 8.50 (d, J = 1.5 Hz, 1H), 8.13 (s, 1H), 7.81 (dd, J = 1.7, 7.9 Hz, 1H), 7.68 (d, J = 9.0 Hz, 1H), 7.57 (s, 1H), 7.37 (ddd, J = 1.3, 6.8, 9.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 6.97 (td, J = 1.1, 6.9 Hz, 1H), 4.83 (s, 2H), 3.80-3.67 (m, 2H), 3.6-3.50 (m, 3H), 2.36 (s, 3H), 1.11 (d, J = 6.0 Hz, 6H). MS m/z 436.2 (M + 1) <sup>+</sup> .	0.081
F34		MS m/z 450.1 (M + 1) <sup>+</sup> .	0.093
F35		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.03 (s, 1H), 9.47-9.44 (m, 1H), 9.18 (t, J = 5.6 Hz, 1H), 8.59 (s, 1H), 8.07 (d, J = 1.6 Hz, 1H), 7.82-7.77 (m, 2H), 7.55-7.50 (m, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.20-7.16 (m, 1H), 4.71 (d, J = 5.6 Hz, 2H), 3.43 (q, J = 11.2 Hz, 2H), 2.37 (s, 3H). MS m/z 459.39 (M + 1) <sup>+</sup> .	0.043
F36		<sup>1</sup> H NMR (400 MHz, d <sub>4</sub> -MeOH) $\delta$ 9.67-9.66 (m, 1H), 8.67 (s, 1H), 8.11 (s, 1H), 7.94-7.89 (m, 2H), 7.83-7.78 (m, 1H), 7.48 (d, J = 8 Hz, 1H), 3.08 (dd, J = 8.0, 6.4 Hz, 2H), 2.45 (s, 3H), 2.03 (dd, J = 8.0, 6.4 Hz, 2H), 1.27 (s, 6H). MS m/z 424.1 (M + 1) <sup>+</sup> .	0.087

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F37		MS m/z 426.1 (M + 1) <sup>+</sup> .	0.092
F38		MS m/z 439.1 (M + 1) <sup>+</sup> .	0.047
F39		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.16 (s, 1H), 9.52-9.50 (m, 1H), 8.69 (s, 1H), 8.10 (d, J = 1.6 Hz, 1H), 7.89-7.86 (m, 1H), 7.85 (dd, J = 2.0, 7.6 Hz, 1H), 7.68-7.64 (m, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.31-7.28 (m, 1H), 5.12 (s, 2H), 4.39-4.32 (m, 2H), 2.38 (s, 3H). MS m/z 432.37 (M + 1) <sup>+</sup> .	0.008
F40		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.11 (s, 1H), 9.51-9.46 (m, 1H), 8.65 (s, 1H), 8.44 (t, J = 6.0 Hz, 1H), 8.07 (d, J = 1.2 Hz, 1H), 7.85-7.08 (m, 2H), 7.63-7.59 (m, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.27-7.24 (m, 1H), 6.39-6.10 (m, 1H), 4.61 (d, J = 5.6 Hz, 2H), 4.35-4.27 (m, 2H), 2.37 (s, 3H). MS m/z 457.14 (M + 1) <sup>+</sup> .	0.071

TABLE 1-continued

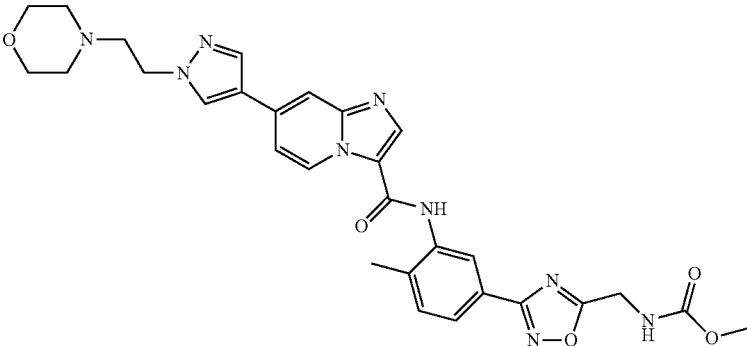
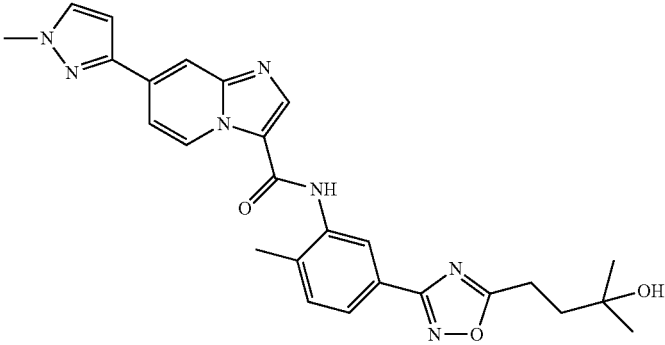
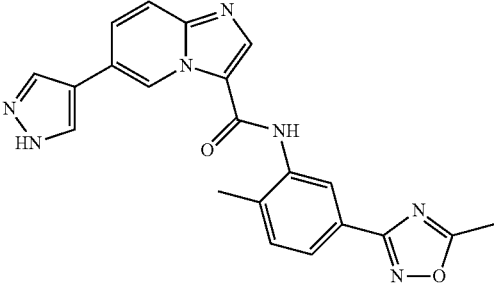
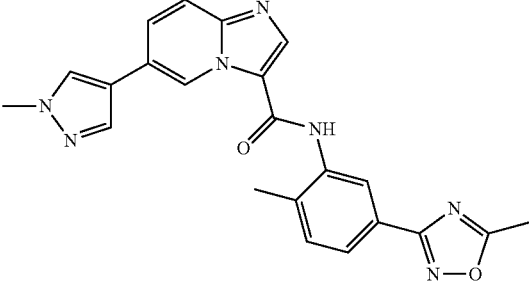
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F41		MS m/z 586.2 (M + 1) <sup>+</sup> .	0.023
F42		MS m/z 486.3 (M + 1) <sup>+</sup> .	0.009
F43		MS m/z 400.1 (M + 1) <sup>+</sup> .	0.046
F44		MS m/z 414.1 (M + 1) <sup>+</sup> .	0.025

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F45		MS m/z 472.1 (M + 1) <sup>+</sup> .	0.024
F46		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.11 (s, 1H), 9.86 (s, 1H), 9.55 (d, J = 6.8 Hz, 1H), 8.86 (s, 1H), 7.95 (d, J = 9.5 Hz, 1H), 7.87-7.83 (m, 1H), 7.45-7.41 (m, 2H), 7.23 (dd, J = 8.0, 2.0 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 3.48 (s, 2H), 2.13 (s, 3H), 1.24 (s, 6H). MS m/z 407.2 (M + 1) <sup>+</sup> .	0.013
F47		MS m/z 417.1 (M + 1) <sup>+</sup> .	0.05
F48		MS m/z 445.1 (M + 1) <sup>+</sup> .	0.007
F49		MS m/z 429.2 (M + 1) <sup>+</sup> .	0.053



TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F50		$^1\text{H NMR}$ (400 MHz, $\text{CDCl}_3$ ) $\delta$ 9.41 (d, $J = 7.2$ Hz, 1H), 8.56 (d, $J = 1.6$ Hz, 1H), 8.15 (s, 1H), 7.86 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.57 (s, 1H), 7.52 (s, 1H), 7.38 (d, $J = 8.0$ Hz, 1H), 6.89 (dd, $J = 1.6, 7.2$ Hz, 1H), 3.11 (m, 2H), 2.49 (s, 3H), 2.43 (s, 3H), 2.09 (m, 2H), 1.74 (s, 1H), 1.34 (s, 6H). MS $m/z$ 420.2 ( $M + 1$ ) $^+$ .	0.052
F51		MS $m/z$ 512.8 ( $M + 1$ ) $^+$ .	0.095
F52		MS $m/z$ 392.2 ( $M + 1$ ) $^+$ .	0.016
F53		$^1\text{H NMR}$ (400 MHz, $d_4$ -MeOH) $\delta$ 8.49 (s, 1H), 8.14 (m, 1H), 7.92 (d, 4.0 Hz, 1H), 7.48 (d, $J = 4.0$ Hz, 1H), 4.90 (s, 2H), 3.82 (m, 2H), 3.62 (m, 2H), 3.36 (s, 3H), 2.42 (s, 3H). MS $m/z$ 412.2 ( $M + 1$ ) $^+$ .	0.061

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F54		$^1\text{H NMR}$ (400 MHz, $d_4$ -MeOH) $\delta$ 8.79 (s, 1H), 8.14 (s, 1H), 7.94 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.50 (d, $J = 7.6$ Hz, 1H), 3.10-3.06 (m, 2H), 2.05-2.01 (m, 2H), 2.04 (s, 3H), 1.27 (s, 6H). MS $m/z$ 410.1 ( $M + 1$ ) $^+$ .	0.097
F55a		$^1\text{H NMR}$ (400 MHz, $\text{CD}_2\text{Cl}_2$ ) $\delta$ 9.85 (d, $J = 6.8$ Hz, 1H), 9.47 (s, 1H), 9.21 (s, 1H), 8.28 (d, $J = 1.6$ Hz, 1H), 8.13 (d, $J = 9.2$ Hz, 1H), 7.94-7.87 (m, 2H), 7.47 (t, $J = 6.8$ Hz, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 5.04 (m, 1H), 3.26 (t, $J = 7.2$ Hz, 2H), 2.91 (t, $J = 7.2$ Hz, 2H), 2.44 (s, 3H), 1.25 (d, $J = 6.4$ Hz, 6H). MS $m/z$ 434.2 ( $M + 1$ ) $^+$ .	0.092
F56		MS $m/z$ 436.1 ( $M + 1$ ) $^+$ .	0.07
F57		MS $m/z$ 420.1 ( $M + 1$ ) $^+$ .	0.098
F58		MS $m/z$ 422.1 ( $M + 1$ ) $^+$ .	0.09

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F59		$^1\text{H NMR}$ (400 MHz, $\text{CD}_2\text{Cl}_2$ ) $\delta$ 9.69 (d, $J = 6.9$ Hz, 1H), 8.84 (s, 1H), 8.64 (s, 1H), 8.47 (d, $J = 1.6$ Hz, 1H), 7.96-7.85 (m, 2H), 7.64 (t, $J = 7.5$ Hz, 1H), 7.44 (d, $J = 8.0$ Hz, 1H), 7.24 (t, $J = 6.9$ Hz, 1H), 3.29-3.16 (m, 1H), 2.49 (s, 3H), 1.95-1.86 (m, 1H), 1.79-1.65 (m, 1H), 1.48-1.44 (m, 3H), 1.44-1.33 (m, 2H), 1.01-0.93 (m, 3H). MS $m/z$ 390.0 ( $M + 1$ ) <sup>+</sup> .	0.022
F60		MS $m/z$ 491.1 ( $M + 1$ ) <sup>+</sup> .	0.058
F61		MS $m/z$ 491.1 ( $M + 1$ ) <sup>+</sup> .	0.272
F62		MS $m/z$ 489.2 ( $M + 1$ ) <sup>+</sup> .	0.079

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F63		MS m/z 486.1 (M + 1) <sup>+</sup> .	0.007
F64		MS m/z 446.1 (M + 1) <sup>+</sup> .	0.048
F65		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.12 (s, 1H), 9.51-9.48 (m, 1H), 8.60 (s, 1H), 7.89 (d, J = 1.6 Hz, 1H), 7.74-7.71 (m, 2H), 7.43 (d, J = 8.0 Hz, 1H), 7.30-7.26 (m, 1H), 3.43 (s, 2H), 3.24 (s, 3H), 2.32 (s, 3H), 1.13 (s, 6H). MS m/z 438.18 (M + 1) <sup>+</sup> .	0.1
F66		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 9.98 (s, 1H), 9.40 (d, J = 6.8 Hz, 1H), 8.54 (s, 1H), 8.01 (d, J = 1.6 Hz, 1H), 7.75 (m, 2H), 7.42-7.48 (m, 2H), 7.12 (dt, J = 0.8, 6.8 Hz, 1H), 6.04 (s, 1H), 3.07 (m, 2H), 2.31 (s, 3H), 1.98-2.17 (m, 2H), 1.25 (s, 3H). MS m/z 460.1 (M + 1) <sup>+</sup> .	0.027

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F67		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 9.96 (s, 1H), 9.32 (d, $J = 7.2$ Hz, 1H), 8.52 (s, 1H), 8.07 (d, $J = 1.6$ Hz, 1H), 7.81 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.04 (dd, $J = 1.6, 7.2$ Hz, 1H), 6.11 (s, 1H), 3.14 (m, 2H), 2.43 (s, 3H), 2.36 (s, 3H), 2.04-2.24 (m, 2H), 1.32 (s, 3H). MS $m/z$ 474.1 ( $M + 1$ ) $^+$ .	0.016
F68		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 9.95 (s, 1H), 9.33-9.31 (m, 1H), 8.72 (t, $J = 5.6$ Hz, 1H), 8.51 (s, 1H), 7.92 (d, $J = 1.6$ Hz, 1H), 7.70 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.56 (s, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.02 (dd, $J = 1.6, 7.2$ Hz, 1H), 4.65-4.63 (m, 1H), 4.54-4.51 (m, 1H), 3.68-3.64 (m, 1H), 3.61-3.57 (m, 1H), 2.42 (s, 3H), 2.33 (s, 3H). MS $m/z$ 394.16 ( $M + 1$ ) $^+$ .	0.054
F69		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 9.95 (s, 1H), 9.33-9.31 (m, 1H), 8.50 (s, 1H), 8.47 (t, $J = 6.0$ Hz, 1H), 7.91 (d, $J = 1.6$ Hz, 1H), 7.69 (dd, $J = 2.0, 8.0$ Hz, 1H), 7.56 (s, 1H), 7.41 (d, $J = 8.0$ Hz, 1H), 7.02 (dd, $J = 1.6, 7.2$ Hz, 1H), 3.12 (t, $J = 6.4$ Hz, 2H), 2.42 (s, 3H), 2.32 (s, 3H), 1.90-1.81 (m, 1H), 0.91 (d, $J = 6.8$ Hz, 6H). MS $m/z$ 404.2 ( $M + 1$ ) $^+$ .	0.016
F70		MS $m/z$ 478.0 ( $M + 1$ ) $^+$ .	0.044

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F71		MS m/z 478.0 (M + 1) <sup>+</sup> .	0.054
F72		MS m/z 474.1 (M + 1) <sup>+</sup> .	0.035
F73		MS m/z 464.1 (M + 1) <sup>+</sup> .	0.025
F74		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.20 (s, 1H), 9.53-9.51 (m, 1H), 8.72 (s, 1H), 8.08 (d, J = 1.6 Hz, 1H), 7.91-7.87 (m, 1H), 7.83 (dd, J = 1.6, 8.0 Hz, 1H), 7.71-7.67 (m, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.34-7.30 (m, 1H), 3.33-3.29 (m, 2H), 2.97-2.85 (m, 2H), 2.37 (s, 3H). MS m/z 415.13 (M + 1) <sup>+</sup> .	0.036

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F75		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 9.96 (s, 1H), 9.32 (d, $J = 7.2$ Hz, 1H), 8.52 (s, 1H), 8.07 (d, $J = 1.6$ Hz, 1H), 7.81 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.04 (dd, $J = 1.6, 7.2$ Hz, 1H), 6.11 (s, 1H), 3.14 (m, 2H), 2.43 (s, 3H), 2.36 (s, 3H), 2.04-2.24 (m, 2H), 1.32 (s, 3H). MS $m/z$ 474.1 ( $M + 1$ ) $^+$ .	0.064
F76		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 9.96 (s, 1H), 9.32 (d, $J = 7.2$ Hz, 1H), 8.52 (s, 1H), 8.07 (d, $J = 1.6$ Hz, 1H), 7.81 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.04 (dd, $J = 1.6, 7.2$ Hz, 1H), 6.11 (s, 1H), 3.14 (m, 2H), 2.43 (s, 3H), 2.36 (s, 3H), 2.04-2.24 (m, 2H), 1.32 (s, 3H). MS $m/z$ 474.1 ( $M + 1$ ) $^+$ .	0.049
F77		$^1\text{H NMR}$ (400 MHz, $\text{CD}_2\text{Cl}_2$ ) $\delta$ 9.97 (s, 1H), 9.34 (d, $J = 6.8$ Hz, 1H), 8.52 (s, 1H), 8.12 (d, $J = 1.6$ Hz, 1H), 7.83 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.58 (s, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.04 (dd, $J = 1.6, 7.2$ Hz, 1H), 5.12 (s, 2H), 4.36 (q, $J = 9.2$ Hz, 2H), 2.43 (s, 3H), 2.37 (s, 3H). MS $m/z$ 446.1 ( $M + 1$ ) $^+$ .	0.01
F78		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 9.97 (s, 1H), 9.33 (d, $J = 7.2$ Hz, 1H), 8.54 (bs, 1H), 8.11 (d, $J = 1.6$ Hz, 1H), 7.84 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.58 (s, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.04 (d, $J = 8.4$ Hz, 1H), 5.12 (s, 2H), 4.36 (q, $J = 8.8$ Hz, 2H), 2.37 (s, 3H). MS $m/z$ 449.1 ( $M + 1$ ) $^+$ .	0.009

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F79		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.0 (s, 1H), 9.30 (s, 1H), 8.55 (s, 1H), 8.13 (d, $J = 1.6$ Hz, 1H), 7.84 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.72 (d, $J = 9.2$ Hz, 1H), 7.52 (d, $J = 8.4$ Hz, 1H), 7.41 (dd, $J = 2.0, 9.2$ Hz, 1H), 5.13 (s, 2H), 4.36 (q, $J = 9.2$ Hz, 2H), 2.38 (s, 6H). MS $m/z$ 446.1 ( $M + 1$ ) $^+$ .	0.013
F80		MS $m/z$ 430.1 ( $M + 1$ ) $^+$ .	0.005
F81		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.12 (s, 1H), 9.42 (s, 1H), 8.68 (s, 1H), 8.06 (d, $J = 1.6$ Hz, 1H), 7.87 (d, $J = 9.2$ Hz, 1H), 7.79 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.64 (dd, $J = 1.6, 9.2$ Hz, 1H), 7.48 (d, $J = 8.0$ Hz, 1H), 7.37-7.31 (m, 4H), 2.65 (s, 3H), 2.36 (s, 3H), 2.28 (s, 3H). MS $m/z$ 423.17 ( $M + 1$ ) $^+$ .	0.096
F82		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.09 (s, 1H), 9.44 (s, 1H), 8.65 (s, 1H), 8.53 (dd, $J = 1.6, 4.8$ Hz, 1H), 8.06 (d, $J = 1.6$ Hz, 1H), 7.88 (dd, $J = 0.8, 9.2$ Hz, 1H), 7.81-7.75 (m, 2H), 7.64 (dd, $J = 2.0, 9.2$ Hz, 1H), 7.48 (d, $J = 8.0$ Hz, 1H), 7.37-7.34 (m, 1H), 2.65 (s, 3H), 2.48 (s, 3H), 2.36 (s, 3H). MS $m/z$ 424.16 ( $M + 1$ ) $^+$ .	0.053



TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F83		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.10 (s, 1H), 9.49 (s, 1H), 8.66 (s, 1H), 8.57 (s, 1H), 8.51-8.50 (m, 1H), 8.06 (d, $J = 1.6$ Hz, 1H), 7.90 (d, $J = 9.2$ Hz, 1H), 7.79 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.64 (dd, $J = 1.6, 9.2$ Hz, 1H), 7.48 (d, $J = 8.0$ Hz, 1H), 7.40-7.39 (m, 1H), 2.65 (s, 3H), 2.36 (s, 3H), 2.31 (s, 3H). MS $m/z$ 424.16 ( $M + 1$ ) <sup>+</sup> .	0.048
F84		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 9.98 (s, 1H), 9.29 (m, 1H), 8.54 (s, 1H), 8.09 (d, $J = 1.6$ Hz, 1H), 7.89 (dd, $J = 2.0, 8.0$ Hz, 1H), 7.70 (dd, $J = 0.8, 9.2$ Hz, 1H), 7.49 (d, $J = 8.4$ Hz, 1H), 7.40 (dd, $J = 2.0, 9.2$ Hz, 1H), 6.11 (s, 1H), 3.05-3.21 (m, 2H), 2.37 (two singlets overlap, 6H), 2.04-2.25 (m, 2H), 1.32 (s, 3H). MS $m/z$ 474.1 ( $M + 1$ ) <sup>+</sup> .	0.03
F85		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.16 (s, 1H), 9.49 (m, 1H), 8.67 (s, 1H), 8.06 (d, $J = 1.6$ Hz, 1H), 7.91 (m, 1H), 7.83 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.69 (m, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 6.11 (s, 1H), 3.13 (m, 2H), 2.37 (s, 3H), 2.04-2.25 (m, 2H), 1.32 (s, 3H). MS $m/z$ 478.0 ( $M + 1$ ) <sup>+</sup> .	0.038
F86		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.15 (s, 1H), 9.49 (m, 1H), 8.66 (s, 1H), 8.06 (d, $J = 1.6$ Hz, 1H), 7.91 (m, 1H), 7.83 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.68 (m, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 6.11 (s, 1H), 3.13 (m, 2H), 2.37 (s, 3H), 2.04-2.25 (m, 2H), 1.32 (s, 3H). MS $m/z$ 478.0 ( $M + 1$ ) <sup>+</sup> .	0.043

TABLE 1-continued

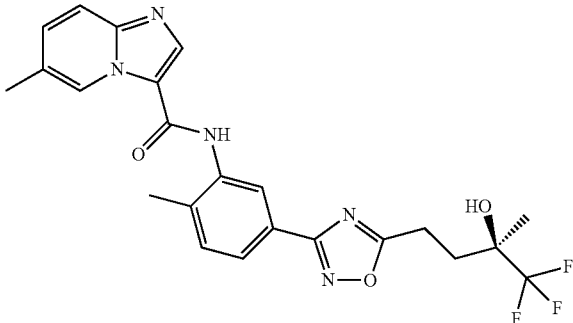
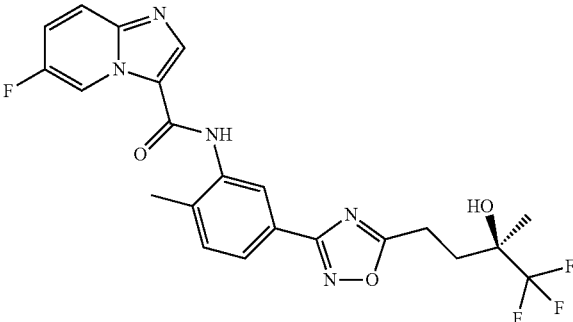
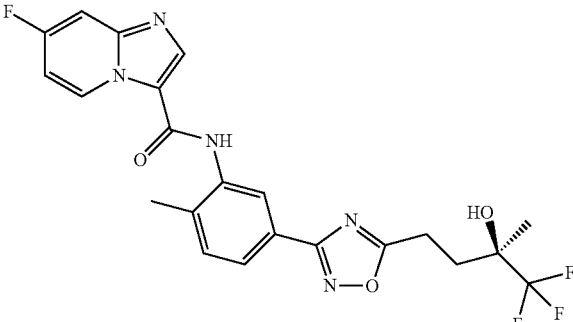
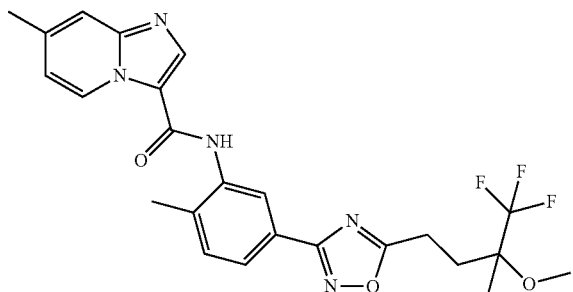
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F87		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 9.98 (s, 1H), 9.29 (m, 1H), 8.54 (s, 1H), 8.09 (d, $J = 1.6$ Hz, 1H), 7.89 (dd, $J = 2.0, 8.0$ Hz, 1H), 7.70 (dd, $J = 0.8, 9.2$ Hz, 1H), 7.49 (d, $J = 8.4$ Hz, 1H), 7.40 (dd, $J = 2.0, 9.2$ Hz, 1H), 6.11 (s, 1H), 3.05-3.21 (m, 2H), 2.37 (two singlets overlap, 6H), 2.04-2.25 (m, 2H), 1.32 (s, 3H). MS $m/z$ 474.1 ( $M + 1$ ) $^+$ .	0.029
F88		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.16 (s, 1H), 9.49 (m, 1H), 8.67 (s, 1H), 8.06 (d, $J = 1.6$ Hz, 1H), 7.91 (m, 1H), 7.83 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.69 (m, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 6.11 (s, 1H), 3.13 (m, 2H), 2.37 (s, 3H), 2.04-2.25 (m, 2H), 1.32 (s, 3H). MS $m/z$ 478.0 ( $M + 1$ ) $^+$ .	0.042
F89		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.15 (s, 1H), 9.49 (m, 1H), 8.66 (s, 1H), 8.06 (d, $J = 1.6$ Hz, 1H), 7.91 (m, 1H), 7.83 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.68 (m, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 6.11 (s, 1H), 3.13 (m, 2H), 2.37 (s, 3H), 2.04-2.25 (m, 2H), 1.32 (s, 3H). MS $m/z$ 478.0 ( $M + 1$ ) $^+$ .	0.041
F90		MS $m/z$ 488.1 ( $M + 1$ ) $^+$ .	0.048

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F91		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.12 (s, 1H), 9.57 (s, 1H), 8.64 (s, 1H), 8.09 (d, $J = 1.6$ Hz, 1H), 7.89-7.83 (m, 2H), 7.60 (dd, $J = 2.0, 9.6$ Hz, 1H), 7.52 (d, $J = 8.0$ Hz, 1H), 5.12 (s, 2H), 4.39-4.32 (m, 2H), 2.65 (s, 3H), 2.41 (s, 3H), 2.37 (s, 3H). MS $m/z$ 542.13 ( $M + 1$ ) <sup>+</sup> .	0.006
F92		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.12 (s, 1H), 9.76 (s, 1H), 8.67 (s, 1H), 8.32-8.25 (m, 2H), 8.09 (d, $J = 1.6$ Hz, 1H), 7.94 (dd, $J = 0.8, 9.2$ Hz, 1H), 7.84-7.79 (m, 2H), 7.55-7.52 (m, 1H), 7.49 (d, $J = 8.0$ Hz, 1H), 2.66 (s, 3H), 2.37 (s, 3H). MS $m/z$ 428.14 ( $M + 1$ ) <sup>+</sup> .	0.016
F93		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.14 (s, 1H), 9.82 (s, 1H), 8.98 (s, 1H), 8.85-8.84 (m, 1H), 8.66 (s, 1H), 8.35-8.32 (m, 1H), 8.14 (d, $J = 8.0$ Hz, 1H), 8.10 (s, 1H), 8.01-7.95 (m, 2H), 7.82-7.80 (m, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 2.84 (d, $J = 4.8$ Hz, 3H), 2.66 (s, 3H), 2.38 (s, 3H). MS $m/z$ 467.17 ( $M + 1$ ) <sup>+</sup> .	0.068
F94		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.15 (s, 1H), 9.52-9.49 (m, 1H), 8.67 (s, 1H), 8.10 (d, $J = 1.6$ Hz, 1H), 7.87-7.84 (m, 2H), 7.67-7.62 (m, 1H), 7.52 (d, $J = 8.4$ Hz, 1H), 7.30-7.26 (m, 1H), 6.40-6.10 (m, 1H), 5.04 (s, 2H), 3.99-3.91 (m, 2H), 2.38 (s, 3H). MS $m/z$ 414.13 ( $M + 1$ ) <sup>+</sup> .	0.039

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F95		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.16 (s, 1H), 9.52-9.50 (m, 1H), 8.68 (s, 1H), 8.10 (d, $J = 1.6$ Hz, 1H), 7.88-7.84 (m, 2H), 7.68-7.63 (m, 1H), 7.52 (d, $J = 8.0$ Hz, 1H), 7.31-7.27 (m, 1H), 5.08 (s, 2H), 4.76-4.73 (m, 1H), 4.66-4.61 (m, 2H), 4.54-4.50 (m, 1H), 4.22-4.09 (m, 1H), 2.37 (s, 3H). MS $m/z$ 428.15 ( $M + 1$ ) $^+$ .	0.028
F96		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.11 (s, 1H), 9.49-9.47 (m, 1H), 8.64 (s, 1H), 8.10 (d, $J = 2.0$ Hz, 1H), 7.85-7.82 (m, 2H), 7.62-7.57 (m, 1H), 7.52 (d, $J = 8.0$ Hz, 1H), 7.26-7.22 (m, 1H), 5.12 (s, 2H), 4.51-4.45 (m, 1H), 2.37 (s, 3H), 1.35 (d, $J = 6.4$ Hz, 3H). MS $m/z$ 446.14 ( $M + 1$ ) $^+$ .	0.011
F97		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.12 (s, 1H), 9.61 (s, 1H), 9.10 (s, 1H), 8.65 (s, 1H), 8.05 (s, 1H), 7.91-7.88 (m, 1H), 7.82-7.80 (m, 1H), 7.67-7.64 (m, 1H), 7.50-7.48 (m, 1H), 2.66 (s, 3H), 2.50 (s, 3H), 2.36 (s, 3H). MS $m/z$ 431.12 ( $M + 1$ ) $^+$ .	0.038
F98		MS $m/z$ 460.1 ( $M + 1$ ) $^+$ .	0.018

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F99		MS m/z 446.0 (M + 1) <sup>+</sup> .	0.045
F100		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.23 (s, 1H), 9.39 (s, 1H), 8.75 (s, 1H), 8.04 (d, J = 1.6 Hz, 1H), 7.94 (dd, J = 0.8, 9.2 Hz, 1H), 7.82 (dd, J = 1.6, 8.0 Hz, 1H), 7.68 (dd, J = 2.0, 9.6 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 3.73 (s, 3H), 2.66 (s, 3H), 2.36 (s, 3H), 2.27 (s, 3H), 2.16 (s, 3H). MS m/z 442.19 (M + 1) <sup>+</sup> .	0.019
F101		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.15 (s, 1H), 9.53 (s, 1H), 8.68 (s, 1H), 8.05 (d, J = 2.0 Hz, 1H), 7.88 (dd, J = 0.8, 9.2 Hz, 1H), 7.83-7.76 (m, 2H), 7.49 (d, J = 8.0 Hz, 1H), 6.95-6.93 (m, 1H), 6.33-6.32 (m, 1H), 6.13-6.11 (m, 1H), 3.70 (s, 3H), 2.66 (s, 3H), 2.36 (s, 3H). MS m/z 413.16 (M + 1) <sup>+</sup> .	0.08
F102		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.14 (s, 1H), 9.69 (s, 1H), 8.84-8.81 (m 2H), 8.67 (s, 1H), 8.08 (d, J = 1.6 Hz, 1H), 7.93 (dd, J = 0.8, 9.2 Hz, 1H), 7.80 (dd, J = 2.0, 8.0 Hz, 1H), 7.74 (dd, J = 1.6, 9.2 Hz, 1H), 7.67-7.66 (m, 1H), 7.49 (d, J = 8.0 Hz, 1H), 4.07 (s, 3H), 2.66 (s, 3H), 2.37 (s, 3H). MS m/z 441.16 (M + 1) <sup>+</sup> .	0.087
F103		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.17 (s, 1H), 9.45 (s, 1H), 8.70 (s, 1H), 8.11 (d, J = 1.6 Hz, 1H), 8.08-8.06 (m, 3H), 7.99 (dd, J = 0.8, 9.6 Hz, 1H), 7.91 (dd, J = 2.0, 9.2 Hz, 1H), 7.83-7.81 (m, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.29-7.27 (m, 2H), 2.67 (s, 3H), 2.39 (s, 3H). MS m/z 426.16 (M + 1) <sup>+</sup> .	0.061



TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F254		MS $m/z$ 513.9 (M + 1) <sup>+</sup> .	0.051
F255		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.10 (s, 1H), 9.36 (s, 1H), 8.65 (s, 1H), 8.04 (s, 1H), 7.86 (d, J = 9.3 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.55 (d, J = 9.3 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 4.06 (t, J = 5.6 Hz, 2H), 3.71 (t, J = 5.6 Hz, 2H), 2.66 (s, 3H), 2.35 (s, 3H), 2.28 (s, 3H), 2.17 (s, 3H). MS $m/z$ 471.20 (M + 1) <sup>+</sup> .	0.016
F256		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.21 (m, 1H), 10.17 (s, 1H), 8.67 (s, 1H), 8.10 (d, J = 1.7 Hz, 1H), 8.02 (dd, J = 1.9, 9.4 Hz, 1H), 7.92 (dd, J = 0.9, 9.4 Hz, 1H), 7.82 (dd, J = 1.8, 7.9 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 2.73 (s, 3H), 2.67 (s, 3H), 2.60 (s, 3H), 2.38 (s, 3H). MS $m/z$ 472.13 (M + 1) <sup>+</sup> .	0.054
F257		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.14 (s, 1H), 9.59 (s, 1H), 8.66 (s, 1H), 8.04 (d, J = 1.7 Hz, 1H), 7.96 (s, 1H), 7.89 (d, J = 9.3 Hz, 1H), 7.82 (dd, J = 1.8, 8.0 Hz, 2H), 7.50 (d, J = 8.1 Hz, 1H), 2.66 (s, 3H), 2.40 (s, 3H), 2.36 (s, 3H), 2.07 (s, 1H). MS $m/z$ 413.16 (M + 1) <sup>+</sup> .	0.019

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F258		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.16 (s, 1H), 10.15-10.14 (m, 1H), 8.68 (s, 1H), 8.27 (d, $J = 4.6$ Hz, 1H), 8.12 (d, $J = 1.7$ Hz, 1H), 7.99 (dd, $J = 1.9, 9.4$ Hz, 1H), 7.92 (dd, $J = 0.9, 9.4$ Hz, 1H), 7.82 (dd, $J = 1.8, 7.9$ Hz, 1H), 7.51 (d, $J = 8.1$ Hz, 1H), 2.76 (d, $J = 4.5$ Hz, 3H), 2.67 (s, 3H), 2.63 (s, 3H), 2.39 (s, 3H). MS $m/z$ 487.14 ( $M + 1$ ) <sup>+</sup> .	0.065
F259		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.16 (s, 1H), 10.15-10.14 (m, 1H), 8.67 (s, 1H), 8.11 (s, 1H), 7.98 (dd, $J = 1.9, 9.4$ Hz, 1H), 7.92 (d, $J = 9.4$ Hz, 1H), 7.84-7.80 (m, 1H), 7.79-7.58 (m, 2H), 7.51 (d, $J = 8.1$ Hz, 1H), 2.67 (s, 3H), 2.64 (s, 3H), 2.38 (s, 3H). MS $m/z$ 473.13 ( $M + 1$ ) <sup>+</sup> .	0.089
F260		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.13 (s, 1H), 9.39 (s, 1H), 8.67 (s, 1H), 8.04 (s, 1H), 8.01 (d, $J = 4.8$ Hz, 1H), 7.89 (d, $J = 9.3$ Hz, 1H), 7.81 (d, $J = 7.9$ Hz, 1H), 7.59 (d, $J = 9.3$ Hz, 1H), 7.49 (d, $J = 8.1$ Hz, 1H), 4.71 (s, 2H), 2.66 (d, $J = 2.3$ Hz, 3H), 2.62 (d, $J = 4.6$ Hz, 3H), 2.36 (s, 3H), 2.23 (s, 3H), 2.17 (s, 3H). MS $m/z$ 498.21 ( $M + 1$ ) <sup>+</sup> .	0.032
F261		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.17 (s, 1H), 9.71-9.69 (m, 1H), 8.68 (s, 1H), 8.06 (d, $J = 1.7$ Hz, 1H), 7.94 (dd, $J = 0.9, 9.3$ Hz, 1H), 7.81 (dd, $J = 1.8, 7.9$ Hz, 1H), 7.75 (dd, $J = 1.9, 9.3$ Hz, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 4.38 (t, $J = 7.1$ Hz, 2H), 2.66 (s, 3H), 2.55 (s, 3H), 2.36 (s, 3H), 1.34 (t, $J = 7.1$ Hz, 3H). MS $m/z$ 502.14 ( $M + 1$ ) <sup>+</sup> .	0.083



TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F262		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.17 (s, 1H), 9.68-9.67 (m, 1H), 9.15 (s, 1H), 8.68 (s, 1H), 8.04 (d, $J = 1.7$ Hz, 1H), 7.94 (d, $J = 9.3$ Hz, 1H), 7.83-7.80 (m, 1H), 7.73-7.69 (m, 1H), 7.50 (d, $J = 8.1$ Hz, 1H), 3.98 (s, 2H), 3.65 (s, 4H), 3.55 (s, 2H), 3.35 (s, 2H), 3.16-3.05 (m, 2H), 2.66 (s, 3H), 2.55 (s, 3H), 2.36 (s, 3H). MS $m/z$ 586.21 ( $M + 1$ ) <sup>+</sup> .	0.075
F263		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.17 (s, 1H), 9.68-9.66 (m, 1H), 8.69 (d, $J = 7.9$ Hz, 2H), 8.05 (d, $J = 1.7$ Hz, 1H), 7.95-7.91 (m, 1H), 7.81 (dd, $J = 1.7, 7.9$ Hz, 1H), 7.72 (dd, $J = 1.9, 9.3$ Hz, 1H), 7.50 (d, $J = 8.1$ Hz, 1H), 3.52 (t, $J = 6.2$ Hz, 2H), 3.35 (t, $J = 6.0$ Hz, 2H), 2.66 (s, 3H), 2.54 (s, 3H), 2.36 (s, 3H). MS $m/z$ 517.15 ( $M + 1$ ) <sup>+</sup> .	0.058
F264		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.16 (s, 1H), 9.67-9.66 (m, 1H), 8.67 (s, 1H), 8.22 (s, 1H), 8.05 (s, 1H), 7.92 (d, $J = 9.3$ Hz, 1H), 7.88 (s, 1H), 7.81 (d, $J = 7.9$ Hz, 1H), 7.71 (d, $J = 11.2$ Hz, 1H), 7.50 (d, $J = 8.1$ Hz, 1H), 2.66 (s, 3H), 2.52 (d, $J = 5.1$ Hz, 3H), 2.36 (s, 3H). MS $m/z$ 473.13 ( $M + 1$ ) <sup>+</sup> .	0.038
F265		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.13 (s, 1H), 9.60-9.59 (m, 1H), 8.65 (s, 1H), 8.05 (s, 1H), 7.89 (d, $J = 9.3$ Hz, 1H), 7.84-7.78 (m, 1H), 7.65 (dd, $J = 1.9, 9.3$ Hz, 1H), 7.49 (d, $J = 8.1$ Hz, 1H), 4.71 (s, 2H), 2.66 (s, 3H), 2.43 (s, 3H), 2.36 (s, 3H). MS $m/z$ 460.13 ( $M + 1$ ) <sup>+</sup> .	0.008

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F266		MS $m/z$ 446.0 ( $M + 1$ ) <sup>+</sup> .	0.011
F267		<sup>1</sup> H NMR (400 MHz, $d_6$ -DMSO) $\delta$ 10.12 (s, 1H), 9.38 (d, $J = 7.1$ Hz, 1H), 8.64 (s, 1H), 8.07 (s, 1H), 7.83 (d, $J = 7.9$ Hz, 1H), 7.67 (s, 1H), 7.50 (d, $J = 8.2$ Hz, 1H), 7.19 (s, 1H), 3.72 (d, $J = 4.2$ Hz, 3H), 3.69 (d, $J = 4.2$ Hz, 3H), 3.36-3.31 (m, 1H), 3.23 (s, 2H), 2.48 (s, 3H), 2.36 (s, 3H), 1.73 (s, 3H), 1.50 (s, 1H). MS $m/z$ 581.17 ( $M + 1$ ) <sup>+</sup> .	0.056
F268		<sup>1</sup> H NMR (400 MHz, $d_6$ -DMSO) $\delta$ 10.14 (s, 1H), 9.40 (d, $J = 7.2$ Hz, 1H), 8.66 (s, 1H), 8.07 (s, 1H), 7.83 (d, $J = 7.9$ Hz, 1H), 7.69 (s, 1H), 7.50 (d, $J = 8.2$ Hz, 1H), 7.21 (s, 1H), 3.23 (d, $J = 5.0$ Hz, 2H), 2.49 (m, 3H), 2.47-2.42 (m, 2H), 2.36 (s, 3H), 1.70 (s, 3H). MS $m/z$ 553.13 ( $M + 1$ ) <sup>+</sup> .	0.026

TABLE 1-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F269		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.20 (s, 1H), 9.42 (d, $J = 7.1$ Hz, 1H), 8.70 (s, 1H), 8.07 (d, $J = 1.6$ Hz, 1H), 7.84 (dd, $J = 1.8, 7.9$ Hz, 1H), 7.73 (s, 1H), 7.51 (d, $J = 8.2$ Hz, 1H), 7.25 (d, $J = 7.1$ Hz, 1H), 3.72 (d, $J = 4.0$ Hz, 3H), 3.69 (d, $J = 4.0$ Hz, 3H), 3.23 (t, $J = 7.0$ Hz, 2H), 2.60-2.54 (m, 2H), 2.49 (s, 3H), 2.36 (s, 3H), 1.73 (s, 3H). MS $m/z$ 581.17 ( $M + 1$ ) <sup>+</sup> .	0.05
F270		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.02 (s, 1H), 9.31 (d, $J = 7.2$ Hz, 1H), 8.54 (s, 1H), 8.01 (d, $J = 1.7$ Hz, 1H), 7.76 (dd, $J = 1.7, 7.9$ Hz, 1H), 7.59 (s, 1H), 7.43 (d, $J = 8.2$ Hz, 1H), 7.08 (d, $J = 7.2$ Hz, 1H), 3.16 (dd, $J = 4.9, 9.9$ Hz, 2H), 2.49 (s, 3H), 2.47-2.44 (m, 2H), 2.30 (s, 3H), 1.63 (s, 3H). MS $m/z$ 553.13 ( $M + 1$ ) <sup>+</sup> .	0.025
F271		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.06 (s, 1H), 9.35 (d, $J = 7.1$ Hz, 1H), 8.61 (s, 1H), 8.31 (s, 2H), 8.07 (s, 1H), 7.82 (dd, $J = 1.7, 7.9$ Hz, 1H), 7.65 (s, 1H), 7.50 (d, $J = 8.2$ Hz, 1H), 7.13 (d, $J = 7.1$ Hz, 1H), 4.27-4.21 (m, 1H), 3.21 (s, 2H), 2.72-2.66 (m, 2H), 2.46 (s, 3H), 2.36 (s, 3H), 1.78 (d, $J = 5.5$ Hz, 3H), 1.42 (dd, $J = 7.2, 9.5$ Hz, 3H). MS $m/z$ 544.20 ( $M + 1$ ) <sup>+</sup> .	0.008

**[0668]** Representative compounds of Formula (I) and Formula (II) with c-kit inhibition  $IC_{50}$  values greater than 100 nM and prepared following the procedures described above, are set forth in Table 2.

TABLE 2

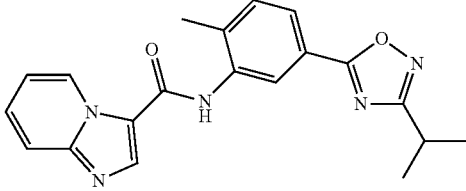
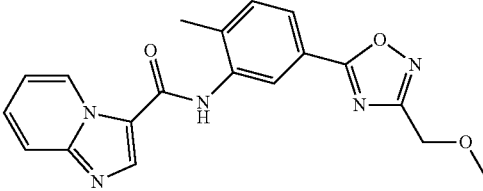
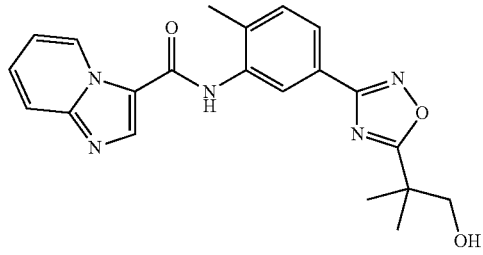
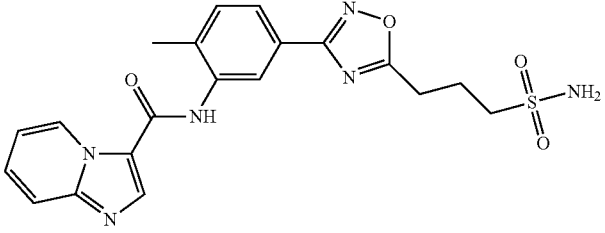
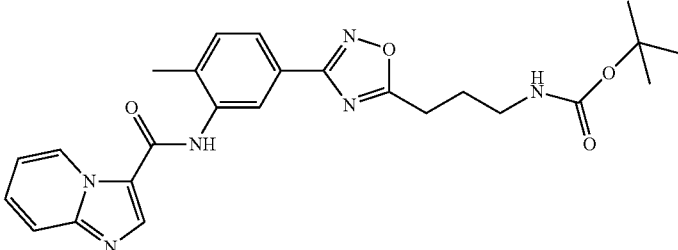
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F107		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.18 (s, 1H), 9.51 (d, $J = 7.2$ Hz, 1H), 8.69 (s, 1H), 8.18 (d, $J = 1.6$ Hz, 1H), 7.91 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.87 (d, $J = 8.8$ Hz, 1H), 7.65 (bt, $J = 7.2$ Hz, 1H), 7.57 (d, $J = 8.0$ Hz, 1H), 7.29 (t, $J = 7.2$ Hz, 1H), 3.15 (hep, 1H), 2.41 (s, 3H), 1.33 (d, $J = 6.8$ Hz, 6H). MS $m/z$ 362.1 ( $M + 1$ ) $^+$ .	0.119
F108		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.16 (s, 1H), 9.50 (d, $J = 7.2$ Hz, 1H), 8.68 (s, 1H), 8.23 (d, $J = 1.6$ Hz, 1H), 7.97 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.86 (d, $J = 8.8$ Hz, 1H), 7.64 (bt, $J = 7.2$ Hz, 1H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.27 (t, $J = 7.2$ Hz, 1H), 1.95 (s, 2H), 3.39 (s, 3H), 2.42 (s, 3H). MS $m/z$ 364.1 ( $M + 1$ ) $^+$ .	0.716*
F109		$^1\text{H NMR}$ (400 MHz, $d_4$ -MeOH) $\delta$ 9.76 (d, $J = 7.2$ Hz, 1H), 8.76 (s, 1H), 8.15 (s, 1H), 7.94 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.57-7.53 (m, 1H), 7.49 (d, $J = 8$ Hz, 1H), 3.77 (s, 2H), 2.43 (s, 3H). MS $m/z$ 392.1 ( $M + 1$ ) $^+$ .	0.682
F110		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.17 (s, 1H), 9.52-9.50 (m, 1H), 8.69 (s, 1H), 8.08-8.06 (m, 1H), 7.88-7.86 (m, 1H), 7.85-7.83 (m, 1H), 7.69-7.65 (m, 1H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.32-7.28 (m, 1H), 6.90 (s, 2H), 3.21-3.14 (m, 4H), 2.37 (s, 3H), 2.27-2.19 (m, 2H). MS $m/z$ 441.48 ( $M + 1$ ) $^+$ .	0.367
F111		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.21 (s, 1H), 9.55-9.51 (m, 1H), 8.73 (s, 1H), 8.06 (d, $J = 1.2$ Hz, 1H), 7.92-7.88 (m, 1H), 7.83 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.74-7.70 (m, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.36-7.32 (m, 1H), 6.95 (t, $J = 6.4$ Hz, 1H), 3.05 (q, $J = 6.8, 12.8$ Hz, 2H), 2.99 (t, $J = 7.2$ Hz, 2H), 2.37 (s, 3H), 1.94-1.87 (m, 2H), 1.36 (s, 9H). MS $m/z$ 477.53 ( $M + 1$ ) $^+$ .	0.364

TABLE 2-continued

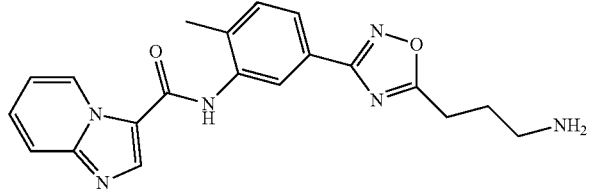
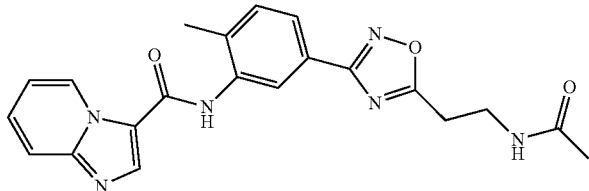
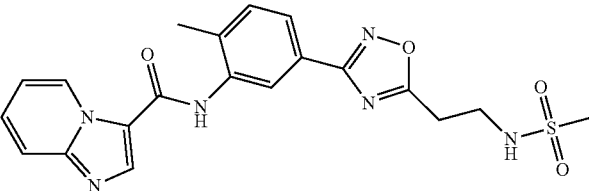
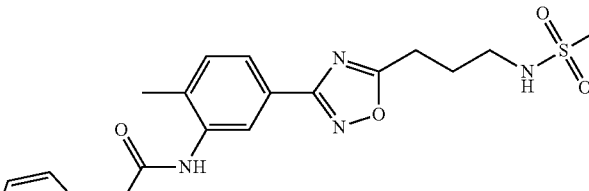
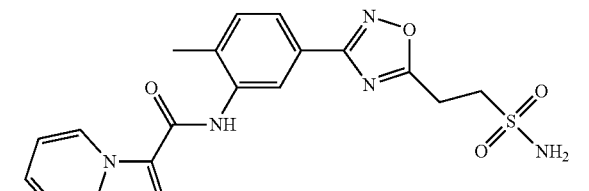
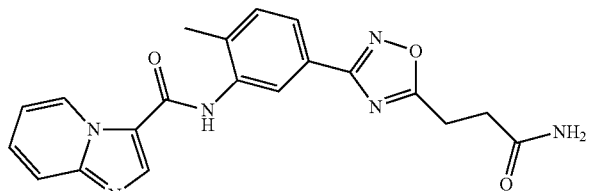
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F112		MS m/z 377.41 (M + 1) <sup>+</sup> .	0.174
F113		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.17 (s, 1 H), 9.53-9.49 (m, 1 H), 8.70 (s, 1 H), 8.14-8.11 (m, 1 H), 8.08 (d, J = 1.6 Hz, 1 H), 7.90-7.86 (m, 1 H), 7.83 (dd, J = 1.6, 8.0 Hz, 1 H), 7.70-7.66 (m, 1 H), 7.51 (d, J = 8.0 Hz, 1 H), 7.31 (t, J = 7.2 Hz, 1 H), 3.63 (q, J = 6.8, 12.8 Hz, 2 H), 3.13 (t, J = 6.8 Hz, 2 H), 2.37 (s, 3 H), 1.79 (s, 3 H). MS m/z 405.42 (M + 1) <sup>+</sup> .	0.689
F114		MS m/z 441.48 (M + 1) <sup>+</sup> .	0.409
F115		MS m/z 445.50 (M + 1) <sup>+</sup> .	0.772
F116		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.14 (s, 1 H), 9.52-9.49 (m, 1 H), 8.68 (s, 1 H), 8.08 (d, J = 1.6 Hz, 1 H), 7.89-7.87 (m, 1 H), 7.83 (dd, J = 1.6, 8.0 Hz, 1 H), 7.67-7.63 (m, 1 H), 7.50 (d, J = 8.4 Hz, 1 H), 7.30- 7.26 (m, 1 H), 7.07 (s, 2 H), 3.58- 3.54 (m, 2 H), 3.46-3.42 (m, 2 H), 2.37 (s, 3 H). MS m/z 427.45 (M + 1) <sup>+</sup> .	0.735
F117		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.16 (s, 1H), 9.51 (d, J = 7.2 Hz, 1H), 8.69 (s, 1H), 8.05 (s, 1H), 7.84 (d, J = 9.2 Hz, 1H), 7.82 (dd, J = 7.6, 1.6 Hz, 1H), 7.64-7.84 (m, 1H), 7.50 (d, J = 8 Hz, 1H), 7.29 (t, J = 7.2 Hz, 1H), 6.94 (s, 1H), 3.15 (t, J = 7.2 Hz, 2H), 2.68 (t, J = 7.2 Hz, 2H), 2.36 (s, 3H). MS m/z 391.40 (M + 1) <sup>+</sup> .	0.803

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F118		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.16 (s, 1H), 9.51 (d, $J = 6.8$ Hz, 1H), 8.70 (s, 1H), 8.05 (s, 1H), 7.88 (d, $J = 9.2$ Hz, 1H), 7.81 (dd, $J = 6.8, 1.5$ Hz, 1H), 7.66 (t, $J = 7.2$ Hz, 1H), 7.50 (d, $J = 8$ Hz, 1H), 7.31 (t, $J = 7.2$ Hz, 1H), 3.15 (t, $J = 7.2$ Hz, 2H), 3.04-3.07 (m, 2H), 2.68 (t, $J = 7.2$ Hz, 2H), 2.36 (s, 3H), 0.99 (t, $J = 7.2$ Hz, 1H). MS $m/z$ 419.45 ( $M + 1$ ) <sup>+</sup> .	0.527
F119		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.12 (s, 1H), 9.50 (d, $J = 6.8$ Hz, 1H), 8.66 (s, 1H), 8.04 (s, 1H), 8.06 (d, $J = 0.8$ Hz, 1H), 7.80-7.87 (m, 2H), 7.63 (t, $J = 8.0$ Hz, 1H), 7.49 (d, $J = 8$ Hz, 1H), 7.26 (t, $J = 6.8$ Hz, 1H), 3.01-3.35 (m, 2H), 2.36 (s, 3H), 1.85-1.91 (m, 2H), 1.14 (s, 6H). MS $m/z$ 406.45 ( $M + 1$ ) <sup>+</sup> .	0.112
F120		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ $^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.17 (s, 1H), 9.52 (d, $J = 6.9$ Hz, 1H), 8.70 (s, 1H), 8.08 (d, $J = 1.6$ Hz), 7.90-7.78 (m, 2H), 7.72-7.63 (m, 1H), 7.51 (d, $J = 8.1$ Hz, 1H), 7.34 (dt, $J = 13.9, 6.3$ Hz, 2H), 3.96 (q, $J = 14.2, 7.1$ Hz, 2H), 3.53-3.40 (m, 2H), 3.14 (t, $J = 6.7$ Hz, 2H), 2.37 (s, 3H), 1.13 (t, $J = 7.1$ Hz). MS $m/z$ 435.45 ( $M + 1$ ) <sup>+</sup> .	0.248
F121		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ $^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.15 (s, 1H), 9.51 (d, $J = 6.9$ , 1H), 8.69 (s, 1H), 8.07 (s, 1H), 7.85 (dd, $J = 8.5, 19.0$ , 2H), 7.66 (s, 1H), 7.50 (d, $J = 8.1$ , 1H), 7.29 (s, 1H), 3.60-3.70 (m, 2H), 2.96-3.10 (m, 2H), 2.37 (s, 3H), 1.77-1.98 (m, 2H), 1.11 (d, $J = 6.2$ , 3H). MS $m/z$ 392.42 ( $M + 1$ ) <sup>+</sup> .	0.104
F122		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ $^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.14 (s, 1H), 8.10 (s, 1H), 7.88-7.81 (m, 2H), 7.68-7.62 (m, 1H), 7.43 (d, $J = 8.1$ , 1H), 7.47-7.39 (m, 1H), 7.28 (s, 1H), 3.44 (s, 4H), 3.39 (t, $J = 6.7$ , 2H), 3.07 (t, $J = 6.7$ , 2H), 2.36 (s, 3H). MS $m/z$ 421.42 ( $M + 1$ ) <sup>+</sup> .	0.326
F123		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ $^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.09 (s, 1H), 9.47 (d, $J = 6.9$ , 1H), 8.63 (s, 1H), 8.05 (s, 1H), 7.81 (t, $J = 7.4$ , 2H), 7.64-7.54 (m, 1H), 7.48 (d, $J = 8.1$ , 2H), 7.23 (s, 1H), 4.04-3.99 (m, 3H), 3.42 (d, $J = 6.2$ , 5H), 3.18 (s, 3H), 3.11 (s, 2H), 2.34 (s, 3H). MS $m/z$ 465.47 ( $M + 1$ ) <sup>+</sup> . MS $m/z$ 350.1 ( $M + 1$ ) <sup>+</sup> .	0.305

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F124		MS $m/z$ 350.1 (M + 1) <sup>+</sup> .	0.217
F125		<sup>1</sup> H NMR (400 MHz, <i>d</i> <sub>6</sub> -DMSO) $\delta$ 10.08 (s, 1 H), 9.47-9.45 (m, 1 H), 8.85 (s, 2 H), 8.66 (s, 1 H), 8.14 (d, <i>J</i> = 1.6 Hz, 1 H), 7.86-7.83 (m, 2 H), 7.62-7.58 (m, 1 H), 7.54 (d, <i>J</i> = 8.0 Hz, 1 H), 7.26-7.23 (m, 1 H), 5.06-5.01 (m, 1 H), 2.39 (s, 3 H), 1.66 (d, <i>J</i> = 7.2 Hz, 3 H). MS $m/z$ 363.39 (M + 1) <sup>+</sup> .	0.889
F126		<sup>1</sup> H NMR (400 MHz, <i>d</i> <sub>6</sub> -DMSO) $\delta$ 10.14 (s, 1 H), 9.52-9.48 (m, 1 H), 8.67 (s, 1 H), 8.07 (d, <i>J</i> = 1.6 Hz, 1 H), 7.87-7.84 (m, 1 H), 7.83-7.78 (m, 2 H), 7.66-7.62 (m, 1 H), 7.50 (d, <i>J</i> = 8.0 Hz, 1 H), 7.29-7.26 (m, 1 H), 5.01-4.93 (m, 1 H), 2.37 (s, 3 H), 1.51 (s, 3 H), 1.40 (s, 9 H). MS $m/z$ 463.50 (M + 1) <sup>+</sup> .	0.102
F127		<sup>1</sup> H NMR (400 MHz, <i>d</i> <sub>6</sub> -DMSO) $\delta$ 10.10 (s, 1 H), 9.48-9.46 (m, 1 H), 8.85 (s, 2 H), 8.67 (s, 1 H), 8.14 (d, <i>J</i> = 1.6 Hz, 1 H), 7.87-7.83 (m, 2 H), 7.64-7.60 (m, 1 H), 7.54 (d, <i>J</i> = 8.4 Hz, 1 H), 7.28-7.24 (m, 1 H), 5.04-5.02 (m, 1 H), 2.39 (s, 3 H), 1.66 (d, <i>J</i> = 7.2 Hz, 3 H). MS $m/z$ 363.39 (M + 1) <sup>+</sup> .	0.196
F128		<sup>1</sup> H NMR (400 MHz, <i>d</i> <sub>6</sub> -DMSO) $\delta$ 10.09 (s, 1 H), 9.50-9.47 (m, 1 H), 8.63 (s, 1 H), 8.09-8.06 (m, 2 H), 7.84-7.80 (m, 2 H), 7.61-7.56 (m, 1 H), 7.50 (d, <i>J</i> = 8.0 Hz, 1 H), 7.25-7.21 (m, 1 H), 4.57 (d, <i>J</i> = 6.0 Hz, 2 H), 3.59 (s, 3 H), 2.37 (s, 3 H). MS $m/z$ 407.39 (M + 1) <sup>+</sup> .	0.113
F129		<sup>1</sup> H NMR (400 MHz, <i>d</i> <sub>6</sub> -DMSO) $\delta$ 10.09 (s, 1 H), 9.49-9.47 (m, 1 H), 8.64 (s, 1 H), 8.11-8.08 (m, 2 H), 7.84-7.81 (m, 2 H), 7.61-7.57 (m, 1 H), 7.51 (d, <i>J</i> = 8.0 Hz, 1 H), 7.25-7.21 (m, 1 H), 4.63 (d, <i>J</i> = 6.0 Hz, 2 H), 3.07 (s, 3), 2.37 (s, 3 H). MS $m/z$ 427.45 (M + 1) <sup>+</sup> .	0.124

TABLE 2-continued

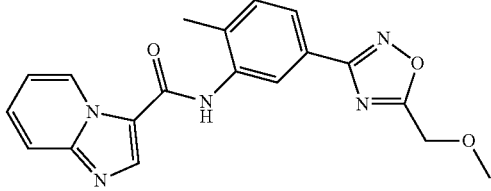
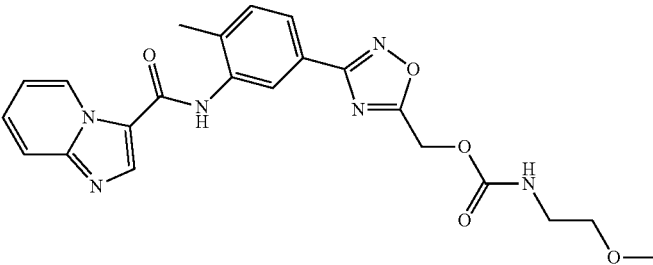
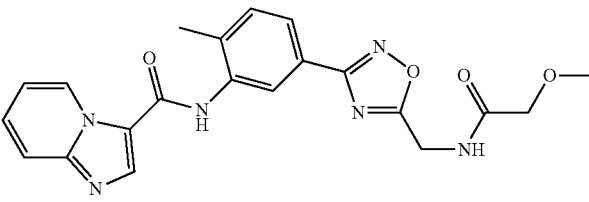
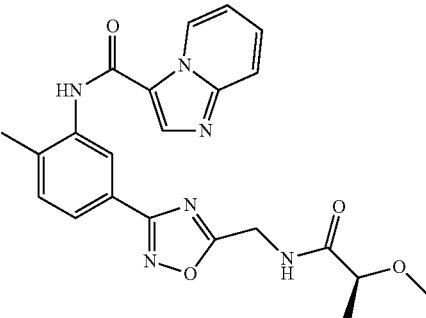
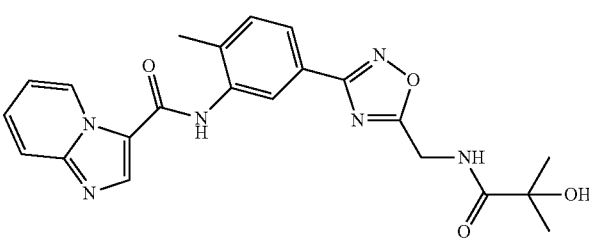
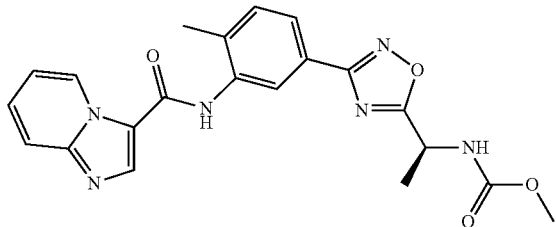
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F130		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.07 (s, 1H), 9.44 (d, $J = 6.9$ , 1H), 8.61 (s, 1H), 8.04 (s, 1H), 7.93-7.83 (m, 2H), 7.58 (s, 1H), 7.45 (d, $J = 8.1$ , 1H), 7.22 (d, $J = 6.9$ , 1H), 4.77 (s, 2H), 3.36 (s, 3H), 2.31 (s, 3H). MS $m/z$ 364.37 ( $M + 1$ ) $^+$ .	0.142
F131		MS $m/z$ 451.1 ( $M + 1$ ) $^+$ .	0.139
F132		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.15 (s, 1H), 9.51 (d, $J = 6.9$ , 1H), 8.70 (d, $J = 14.6$ , 2H), 8.07 (s, 1H), 7.88-7.79 (m, 2H), 7.67 (s, 1H), 7.51 (d, $J = 8.1$ , 1H), 7.30 (s, 1H), 4.65 (s, 2H), 3.92 (s, 3H), 3.36 (s, 2H), 2.37 (s, 3H). MS $m/z$ 421.42 ( $M + 1$ ) $^+$ .	0.319
F133		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.12 (s, 1H), 9.50 (d, $J = 6.9$ , 1H), 8.74 (s, 1H), 8.66 (s, 1H), 8.07 (s, 1H), 7.89-7.77 (m, 2H), 7.68-7.59 (m, 1H), 7.51 (d, $J = 8.1$ , 1H), 7.26 (s, 1H), 4.62 (d, $J = 5.7$ , 2H), 3.63 (t, $J = 6.5$ , 3H), 2.43-2.26 (m, 6H). MS $m/z$ 435.45 ( $M + 1$ ) $^+$ .	0.183
F134		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.13 (s, 1H), 9.49 (d, $J = 6.9$ , 1H), 8.66 (s, 1H), 8.57 (s, 1H), 8.07 (s, 1H), 7.83 (dd, $J = 9.3$ , 18.5, 2H), 7.72- 7.55 (m, 1H), 7.51 (d, $J = 8.1$ , 1H), 7.27 (s, 1H), 4.60 (d, $J = 5.9$ , 2H), 2.37 (s, 3H), 1.28 (s, 6H). MS $m/z$ 435.45 ( $M + 1$ ) $^+$ .	0.173
F135		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.16 (s, 1 H), 9.52-9.50 (m, 1 H), 8.68 (s, 1 H), 8.13-8.10 (m, 1 H), 8.06 (d, $J = 2.0$ Hz, 1 H), 7.88-7.84 (m, 1 H), 7.82 (dd, $J = 2.0$ , 8.0 Hz, 1 H), 7.68-7.63 (m, 1 H), 7.51 (d, $J =$ 8.0 Hz, 1 H), 7.31-7.27 (m, 1 H), 5.07-5.00 (m, 1 H), 3.57 (s, 3 H), 2.37 (s, 3 H), 1.54 (d, $J = 7.2$ Hz, 3 H). MS $m/z$ 421.42 ( $M + 1$ ) $^+$ .	0.166



TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F136		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.17 (s, 1 H), 9.52-9.50 (m, 1 H), 8.69 (s, 1 H), 8.18 (d, $J = 7.6$ Hz, 1 H), 8.08 (d, $J = 2.0$ Hz, 1 H), 7.88- 7.85 (m, 1 H), 7.84 (dd, $J = 2.0$ , 8.0 Hz, 1 H), 7.68-7.64 (m, 1 H), 7.52 (d, $J = 8.0$ Hz, 1 H), 7.31-7.28 (m, 1 H), 5.06-4.99 (m, 1 H), 3.04 (s, 3 H), 2.37 (s, 3H), 1.58 (d, $J = 7.2$ Hz, 3 H). MS $m/z$ 441.48 ( $M + 1$ ) <sup>+</sup> .	0.145
F137		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.18 (s, 1 H), 9.53-9.50 (m, 1 H), 8.69 (s, 1 H), 8.13-8.10 (m, 1 H), 8.06 (d, $J = 1.6$ Hz, 1H), 7.89-7.86 (m, 1 H), 7.82 (dd, $J = 1.6$ , 7.6 Hz, 1 H), 7.69-7.65 (m, 1 H), 7.51 (d, $J =$ 8.0 Hz, 1 H), 7.32-7.28 (m, 1 H), 5.07-5.00 (m, 1 H), 3.57 (s, 3 H), 2.37 (s, 3H), 1.54 (d, $J = 7.2$ Hz, 3 H). MS $m/z$ 421.42 ( $M + 1$ ) <sup>+</sup> .	0.193
F138		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.16 (s, 1 H), 9.52-9.49 (m, 1 H), 8.68 (s, 1 H), 8.07 (d, $J = 1.6$ Hz, 1 H), 7.88-7.84 (m, 1 H), 7.83 (dd, $J =$ 2.0, 8.0 Hz, 1 H), 7.68-7.63 (m, 1 H), 7.50 (d, $J = 8.0$ Hz, 1 H), 7.31- 7.27 (m, 1 H), 3.09 (s, 2 H), 2.37 (s, 3 H), 1.27 (s, 6 H). MS $m/z$ 392.42 ( $M + 1$ ) <sup>+</sup> .	0.233
F139		MS $m/z$ 396.1 ( $M + 1$ ) <sup>+</sup> .	0.394
F140		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.16 (s, 1H), 9.51 (d, $J = 7.0$ , 1H), 8.74 (d, $J = 7.2$ , 1H), 8.68 (s, 1H), 8.06 (d, $J = 1.7$ , 1H), 7.87 (d, $J = 9.0$ , 1H), 7.89-7.84 (m, 2 H), 7.69-7.63 (m, 1H), 7.51 (d, $J = 8.1$ , 1H), 7.29 (t, $J = 6.9$ , 1H), 5.20 (q, $J = 7.2$ , 1H), 2.37 (s, 3H), 1.89 (s, 3H), 1.53 (d, $J = 7.2$ , 3H). MS $m/z$ 405.42 ( $M + 1$ ) <sup>+</sup> .	1.337
F141		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.19 (s, 1H), 9.52 (d, $J = 7.0$ , 1H), 8.78 (t, $J = 5.7$ , 1H), 8.71 (s, 1H), 7.89- 7.84 (m, 2 H), 7.75-7.65 (m, 1H), 7.51 (d, $J = 8.1$ , 1H), 7.32 (t, $J = 6.4$ , 1H), 4.60 (d, $J = 5.7$ , 2H), 2.37 (s, 3H), 1.92 (s, 3H). MS $m/z$ 391.40 ( $M + 1$ ) <sup>+</sup> .	0.867

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F142		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.11 (s, 1H), 9.50 (d, $J = 6.9$ , 1H), 8.66 (s, 1H), 7.69-7.57 (m, 1H), 7.49 (d, $J = 8.0$ , 1H), 7.26 (s, 1H), 7.04- 6.96 (m, 1H), 4.01-3.93 (m, 2H), 3.01-3.15 (m, 1H), 2.36 (s, 3H), 1.30 (s, 9H), 1.16 (d, $J = 6.7$ , 3H). MS $m/z$ 477.53 ( $M + 1$ ) <sup>*</sup> .	0.294
F143		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.18 (s, 1H), 9.52 (d, $J = 7.0$ , 1H), 8.70 (s, 1H), 8.05 (s, 1H), 7.81-7.91 (m, 3H), 7.71-7.59 (m, 1H), 7.50 (d, $J = 8.1$ , 1H), 7.31 (t, $J = 6.5$ , 1H), 2.37 (s, 3H), 1.62 (s, 5H), 1.34 (s, 9H). MS $m/z$ 477.53 ( $M + 1$ ) <sup>*</sup> .	0.201
F144		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.16 (s, 1H), 9.50 (d, $J = 6.9$ , 1H), 8.68 (s, 1H), 8.09 (d, $J = 1.7$ , 1H), 7.89- 7.82 (m, 2H), 7.68-7.61 (m, 1H), 7.52 (d, $J = 8.1$ , 1H), 7.28 (t, $J = 6.5$ , 1H), 4.80 (s, 2H), 3.07 (s, 3H), 2.96 (s, 3H), 2.37 (s, 3H). MS $m/z$ 441.48 ( $M + 1$ ) <sup>*</sup> .	0.156
F145		MS $m/z$ 377.41 ( $M + 1$ ) <sup>*</sup> .	0.219
F146		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.11 (s, 1H), 9.50 (d, $J = 6.9$ , 1H), 8.66 (s, 1H), 8.10 (d, $J = 1.7$ , 1H), 7.93- 7.79 (m, 2H), 7.65-7.59 (m, 1H), 7.51 (d, $J = 8.1$ , 1H), 7.26 (t, $J = 6.9$ , 1H), 4.25 (s, 2H), 2.37 (s, 3H). MS $m/z$ 378.35 ( $M + 1$ ) <sup>*</sup> .	0.381

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F147		MS m/z 455.50 (M + 1) <sup>+</sup> .	0.457
F148		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.21 (s, 1H), 9.53 (d, J = 7.0, 1H), 8.71 (s, 1H), 8.17 (s, 1H), 8.04 (d, J = 1.7, 1H), 7.94-7.77 (m, 2H), 7.72- 7.64 (m, 1H), 7.51 (d, J = 8.1, 1H), 7.32 (t, J = 6.9, 1H), 3.50 (s, 3H), 2.37 (s, 3H), 1.65 (s, 6H). MS m/z 433.45 (M + 1) <sup>+</sup> .	0.208
F149		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.14 (s, 1H), 9.50 (d, J = 6.9, 1H), 8.68 (s, 1H), 8.08 (s, 1H), 7.92-7.78 (m, 2H), 7.65 (s, 1H), 7.51 (d, J = 8.1, 1H), 7.40-7.19 (m, 2H), 3.17 (d, J = 6.8, 2H), 2.89 (s, 3H), 2.37 (s, 3H), 1.27 (d, J = 6.6, 3H). MS m/z 455.50 (M + 1) <sup>+</sup> .	0.22
F150		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.15 (s, 1H), 9.50 (d, J = 7.0, 1H), 8.68 (s, 1H), 8.06 (s, 1H), 7.94-7.77 (m, 2H), 7.65 (s, 1H), 7.50 (d, J = 8.1, 1H), 7.28 (s, 2H), 3.48 (s, 4H), 3.13 (d, J = 6.2, 2H), 2.37 (s, 3H), 1.18 (d, J = 6.7, 3H). MS m/z 435.45 (M + 1) <sup>+</sup> .	0.196

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F151		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ $\delta$ 10.21 (s, 1H), 9.53 (d, $J = 7.0$ , 1H), 8.71 (s, 1H), 8.17 (s, 1H), 8.04 (d, $J = 1.7$ , 1H), 7.94-7.77 (m, 2H), 7.72- 7.64 (m, 1H), 5.03 (s, 2H), 3.57- 3.71 (m, 3H), 3.22 (s, 3H), 2.37 (s, 3H), 1.79-1.98 (m, 3H). MS $m/z$ 517.47 ( $M + 1$ ) $^+$ .	0.134
F152		MS $m/z$ 453.2 ( $M + 1$ ) $^+$ .	0.207
F153		MS $m/z$ 504.1 ( $M + 1$ ) $^+$ .	0.246
F154		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.15 (s, 1H), 9.51 (d, $J = 7.0$ , 1H), 8.97 (s, 1H), 8.69 (s, 1H), 8.07 (s, 1H), 7.87 (d, $J = 9.0$ , 1H), 7.84-7.79 (m, 1H), 7.67 (s, 1H), 7.51 (d, $J = 8.1$ , 1H), 7.30 (s, 1H), 4.66 (d, $J = 5.7$ , 2H), 2.51 (s, 2H), 2.37 (s, 3H). MS $m/z$ 473.42 ( $M + 1$ ) $^+$ .	0.182
F155		MS $m/z$ 426.2 ( $M + 1$ ) $^+$ .	0.396

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F156		MS m/z 467.0 (M + 1) <sup>+</sup> .	0.198
F157		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.15 (s, 1H), 9.51 (d, J = 6.9, 1H), 8.68 (s, 1H), 8.24 (s, 1H), 8.07 (s, 1H), 7.89-7.78 (m, 2H), 7.69-7.61 (m, 1H), 7.51 (d, J = 8.1, 1H), 7.29 (t, J = 6.9, 1H), 4.68-4.63 (m, 1H), 4.59 (d, J = 5.9, 2H), 4.55-4.52 (m, 1H), 4.31-4.27 (m, 1H), 4.23-4.19 (m, 2H), 2.37 (s, 3H). MS m/z 439.41 (M + 1) <sup>+</sup> .	0.155
F158		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 8.78 (dd, J = 1.4, 4.6, 1H), 8.07 (d, J = 11.4, 1H), 8.03-7.91 (m, 3H), 7.77-7.67 (m, 3H), 7.63-7.54 (m, 1H), 7.51 (s, 1H), 3.34 (s, 5H), 2.77 (d, J = 11.6, 3H). MS m/z 432.1 (M + 1) <sup>+</sup> .	0.779
F159		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.14 (s, 1H), 9.49 (dd, J = 2.2, 4.8, 1H), 8.66 (s, 1H), 8.07 (d, J = 1.7, 2H), 7.90 (dd, J = 5.0, 10.1, 1H), 7.82 (dd, J = 1.7, 7.9, 1H), 7.72-7.62 (m, 1H), 7.51 (d, J = 8.1, 1H), 4.58 (d, J = 6.0, 2H), 2.37 (s, 3H). MS m/z 425.1 (M + 1) <sup>+</sup> .	0.184
F160		MS m/z 370.0 (M + 1) <sup>+</sup> .	0.48

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F161		MS m/z 352.1 (M + 1) <sup>+</sup> .	0.173
F162		MS m/z 418.1 (M + 1) <sup>+</sup> .	0.266
F163		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.17 (s, 1 H), 9.53-9.50 (m, 1H), 8.70 (s, 1 H), 8.11 (d, J = 1.6 Hz, 1 H), 7.89-7.86 (m, 1 H), 7.85 (dd, J = 1.6, 8.0 Hz, 1 H), 7.70-7.65 (m, 1 H), 7.52 (d, J = 8.0 Hz, 1 H), 7.32-7.28 (m, 1 H), 4.91 (s, 2 H), 3.64-3.62 (m, 2 H), 3.58-3.55 (m, 2 H), 2.38 (s, 3 H). MS m/z 394.40 (M + 1) <sup>+</sup> .	0.192
F164		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.19 (s, 1 H), 9.54-9.51 (m, 1 H), 8.71 (s, 1 H), 8.07 (d, J = 1.6 Hz, 1 H), 7.90-7.87 (m, 1 H), 7.82 (dd, J = 1.6, 8.0 Hz, 1 H), 7.72-7.67 (m, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.34-7.30 (m, 1 H), 7.25 (t, J = 5.2 Hz, 1 H), 4.51 (d, J = 5.2 Hz, 2 H), 2.82 (s, 6 H), 2.37 (s, 3 H). MS m/z 420.44 (M + 1) <sup>+</sup> .	0.965
F165		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.15 (s, 1 H), 9.53-9.50 (m, 1 H), 8.68 (s, 1 H), 8.13 (t, J = 5.6 Hz, 1 H), 8.07 (d, J = 1.6 Hz, 1 H), 7.89-7.85 (m, 1 H), 7.82 (dd, J = 1.6, 8.0 Hz, 1 H), 7.69-7.64 (m, 1 H), 7.50 (d, J = 8.4 Hz, 1 H), 7.31-7.27 (m, 1 H), 4.57 (d, J = 6.0 Hz, 2 H), 4.13-4.10 (m, 2 H), 3.25 (s, 3), 3.51-3.49 (m, 2 H), 2.37 (s, 3 H). MS m/z 451.45 (M + 1) <sup>+</sup> .	0.512

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F166		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.14 (s, 1 H), 9.52-9.50 (m, 1 H), 8.85 (t, $J = 5.6$ Hz, 1 H), 8.68 (s, 1 H), 8.07 (d, $J = 1.6$ Hz, 1 H), 7.38-7.85 (m, 1 H), 7.81 (dd, $J = 1.6, 8.0$ Hz, 1 H), 7.68-7.64 (m, 1 H), 7.50 (d, $J =$ 8.4 Hz, 1 H), 7.31-7.27 (m, 1 H), 4.64 (d, $J = 5.6$ Hz, 2 H), 4.06-3.99 (m, 4 H), 3.83-3.80 (m, 2 H), 2.37 (s, 3 H). MS $m/z$ 503.45 ( $M + 1$ ) <sup>+</sup> .	0.213
F167		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.12 (s, 1 H), 9.48-9.46 (m, 1 H), 8.63 (s, 1 H), 8.07 (t, $J = 5.6$ Hz, 1 H), 8.06 (d, $J = 1.6$ Hz, 1 H), 7.90-7.86 (m, 1 H), 7.82 (dd, $J = 2.0, 8.0$ Hz, 1 H), 7.67-7.62 (m, 1 H), 7.50 (d, $J =$ 8.0 Hz, 1 H), 4.57 (d, $J = 6.0$ Hz, 2 H), 3.59 (s, 3 H), 2.36 (s, 3 H). MS $m/z$ 425.39 ( $M + 1$ ) <sup>+</sup> .	0.166
F168		MS $m/z$ 432.0 ( $M + 1$ ) <sup>+</sup> .	0.22
F169		MS $m/z$ 424.1 ( $M + 1$ ) <sup>+</sup> .	0.142
F170		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.24 (s, 1 H), 9.63-9.60 (m, 1 H), 8.75 (s, 1 H), 8.33-8.30 (m, 1 H), 8.09-8.06 (m, 2 H), 7.83 (dd, $J =$ 2.0, 8.0 Hz, 1 H), 7.51 (d, $J = 8.4$ Hz, 1 H), 7.46 (dd, $J = 2.0, 7.6$ Hz, 1 H), 4.56 (d, $J = 6.0$ Hz, 2 H), 3.59 (s, 3 H), 2.37 (s, 3 H). MS $m/z$ 475.39 ( $M + 1$ ) <sup>+</sup> .	0.462

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F171		MS m/z 459.2 (M + 1) <sup>+</sup> .	0.182
F172		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.01 (s, 1 H), 9.47-9.45 (m, 1 H), 8.59 (s, 1 H), 8.08 (d, J = 1.6 Hz, 1 H), 7.82 (dd, J = 1.6, 8.0 Hz, 1 H), 7.80-7.78 (m, 1 H), 7.55-7.50 (m, 1 H), 7.51 (d, J = 8.0 Hz, 1 H), 7.20-7.16 (m, 1 H), 5.46 (s, 2 H), 2.37 (s, 3 H), 2.17 (s, 3 H). MS m/z 392.38 (M + 1) <sup>+</sup> .	0.156
F173		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.15 (s, 1 H), 9.52-9.48 (m, 1 H), 8.67 (s, 1 H), 8.07 (d, J = 1.6 Hz, 1 H), 7.87-7.82 (m, 2 H), 7.66-7.62 (m, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.29-7.26 (m, 1 H), 2.37 (s, 3 H), 1.61 (s, 6 H). MS m/z 378.15 (M + 1) <sup>+</sup> .	0.281
F174		MS m/z 377.2 (M + 1) <sup>+</sup> .	0.284
F175		NMR (400 MHz, d <sub>3</sub> -CH <sub>3</sub> CN 1H) $\delta$ = 9.49 (dd, J = 2.4, 4.7, 1H), 8.60 (s, 1H), 8.44 (s, 1H), 8.15 (dd, J = 1.8, 7.2, 1H), 7.86 (dd, J = 5.0, 9.8, 1H), 7.80 (dd, J = 1.7, 7.9, 1H), 7.58 (ddd, J = 2.5, 7.9, 10.1, 1H), 7.39 (d, J = 8.0, 1H), 4.80-4.72 (m, 2H), 3.97-3.81 (m, 2H), 3.72 (s, 4H), 2.32 (d, J = 4.4, 3H). MS m/z 494.0 (M + 1) <sup>+</sup> .	0.104



TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F176		MS $m/z$ 502.1 ( $M + 1$ ) <sup>+</sup> .	0.226
F177		<sup>1</sup> H NMR (400 MHz, <i>d</i> <sub>6</sub> -DMSO) $\delta$ 10.13 (s, 1 H), 9.40-9.38 (m, 1 H), 8.65 (s, 1 H), 8.09-8.06 (m, 2 H), 7.81 (dd, <i>J</i> = 1.6, 8.0 Hz, 1 H), 7.68-7.65 (m, 1 H), 7.50 (d <i>J</i> = 8.0 Hz, 1 H), 7.26-7.22 (m, 1 H), 4.57 (d, <i>J</i> = 6.0 Hz, 1 H), 3.59 (s, 3 H), 2.93-2.91 (m, 4 H), 2.36 (s, 3H), 2.13 (s, 3 H). MS $m/z$ 477.18 ( $M + 1$ ) <sup>+</sup> .	0.24
F178		<sup>1</sup> H NMR (400 MHz, <i>d</i> <sub>6</sub> -DMSO) $\delta$ 10.13 (s, 1 H), 9.42-9.39 (m, 1 H), 8.65 (s, 1 H), 8.09-8.06 (m, 2 H), 7.83-7.80 (m, 1 H), 7.67 (s, 1 H), 7.52-7.50 (m, 1 H), 7.23-7.21 (m, 1 H), 4.57 (d, <i>J</i> = 6.0 Hz, 2 H), 3.59 (s, 3 H), 2.82-2.78 (m, 2 H), 2.37 (s, 3 H), 1.74-1.70 (m, 2 H), 1.17 (s, 6 H). MS $m/z$ 493.21 ( $M + 1$ ) <sup>+</sup> .	0.279
F179		<sup>1</sup> H NMR (400 MHz, <i>d</i> <sub>4</sub> -MeOH) $\delta$ 9.68 (s, 1 H), 8.70 (s, 1 H), 8.15 (d, <i>J</i> = 1.6 Hz, 1 H), 7.96-7.91 (m, 2 H), 7.84-7.79 (m, 1 H), 7.50 (d, <i>J</i> = 8.0 Hz, 1 H), 3.82 (dd, <i>J</i> = 6.4, 4.4 Hz, 2 H), 3.62 (dd, <i>J</i> = 6.4, 4.4 Hz, 2 H), 3.36 (s, 3 H), 2.43 (s, 3 H). MS $m/z$ 426.1 ( $M + 1$ ) <sup>+</sup> .	0.139
F180		<sup>1</sup> H NMR (400 MHz, <i>d</i> <sub>6</sub> -DMSO) $\delta$ 10.12 (s, 1 H), 9.36 (s, 1 H), 8.66 (s, 1 H), 8.09 (d, <i>J</i> = 1.6 Hz, 1 H), 7.83-7.80 (m, 2 H), 7.61 (dd, <i>J</i> = 1.6, 9.2 Hz, 1H), 7.49 (d, <i>J</i> = 8.0 Hz, 1H), 2.88-2.86 (m, 4 H), 2.67 (s, 3 H), 2.37 (s, 3 H), 2.11 (s, 3 H). MS $m/z$ 404.16 ( $M + 1$ ) <sup>+</sup> .	0.356

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F181		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.12 (s, 1 H), 9.35 (s, 1 H), 8.67 (s, 1 H), 8.09 (d, $J = 1.6$ Hz, 1 H), 7.82-7.79 (m, 2 H), 7.62-7.59 (m, 1 H), 7.49 (d, $J = 8.0$ Hz, 1 H), 2.77-2.73 (m, 2 H), 2.67 (s, 3 H), 2.37 (s, 3 H), 1.72-1.67 (m, 2 H), 1.16 (s, 6 H). MS $m/z$ 420.20 ( $M + 1$ ) $^+$ .	0.287
F182		MS $m/z$ 550.1 ( $M + 1$ ) $^+$ .	0.328
F183		MS $m/z$ 548.2 ( $M + 1$ ) $^+$ .	0.394
F184		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 9.98 (s, 1H), 9.36 (s, 1H), 8.55 (s, 1H), 8.08 (d, $J = 1.6$ Hz, 1H), 7.80 (dd, $J = 2.0, 8.0$ Hz, 1H), 7.71 (dd, $J = 0.8, 9.2$ Hz, 1H), 7.49-7.45 (m, 2H), 4.43 (s, 1H), 3.57-3.55 (m, 4H), 3.05-3.01 (m, 2H), 2.85-2.81 (m, 2H), 2.58-2.54 (m, 2H), 2.45-2.41 (m, 4H), 2.36 (s, 3H), 1.91-1.87 (m, 2H), 1.14 (s, 6H). MS $m/z$ 518.26 ( $M + 1$ ) $^+$ .	0.158
F185		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.24 (s, 1H), 9.94 (s, 1H), 8.71 (s, 1H), 8.08 (d, $J = 1.6$ Hz, 1H), 7.96 (dd, $J = 0.8, 9.2$ Hz, 1H), 7.83-7.79 (m, 2H), 7.50 (d, $J = 7.6$ Hz, 1H), 2.67 (s, 3H), 2.37 (s, 3H). MS $m/z$ 358.12 ( $M + 1$ ) $^+$ .	0.508

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F186		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.06 (s, 1H), 9.49 (s, 1H), 8.62 (s, 1H), 8.11 (s, 1H), 7.84 (d, $J = 9.2$ Hz, 1H), 7.81 (dd, $J = 2.0, 8.0$ Hz, 1H), 7.60-7.57 (m, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 4.06-3.95 (m, 1H), 3.80-3.63 (m, 3H), 3.41-3.34 (m, 3H), 3.26-3.01 (m, 2H), 2.67 (s, 3H), 2.38 (s, 3H), 1.25-1.23 (m, 2H). MS $m/z$ 460.22 ( $M + 1$ ) <sup>+</sup> .	0.416
F187		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.26 (s, 1H), 9.53 (dd, $J = 0.8, 7.2$ Hz, 1H), 8.77 (s, 1H), 8.58-8.57 (m, 1H), 8.06 (d, $J = 1.6$ Hz, 1H), 7.82 (dd, $J = 2.0, 8.0$ Hz, 1H), 7.51-7.47 (m, 2H), 2.66 (s, 3H), 2.36 (s, 3H). MS $m/z$ 358.12 ( $M + 1$ ) <sup>+</sup> .	0.219
F188		MS $m/z$ 438.1 ( $M + 1$ ) <sup>+</sup> .	0.103
F189		MS $m/z$ 362.1 ( $M + 1$ ) <sup>+</sup> .	0.122
F190		MS $m/z$ 422.1 ( $M + 1$ ) <sup>+</sup> .	0.119

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F191		MS m/z 491.1 (M + 1) <sup>+</sup>	0.272
F192		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.10 (s, 1H), 9.51-9.48 (m, 1H), 8.60 (s, 1H), 8.40-8.37 (m, 1H), 7.90 (d, J = 1.6 Hz, 1H), 7.75-7.69 (m, 2H), 7.43 (d, J = 8.0 Hz, 1H), 7.30-7.26 (m, 1H), 3.25 (d, J = 6.0 Hz, 2H), 2.32 (s, 3H), 1.23 (s, 6H). MS m/z 424.17 (M + 1) <sup>+</sup> .	0.313
F193		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.15 (s, 1H), 9.36 (s, 1H), 8.67 (s, 1H), 8.38 (t, J = 6.4 Hz, 1H), 7.93 (d, J = 1.6 Hz, 1H), 7.83-7.81 (m, 1H), 7.70 (dd, J = 1.6, 8.0 Hz, 1H), 7.61- 7.59 (m, 1H), 7.43 (d, J = 8.4 Hz, 1H), 3.25 (d, J = 6.0 Hz, 2H), 2.41 (s, 3H), 2.34 (s, 3H), 1.13 (s, 6H). MS m/z 420.19 (M + 1) <sup>+</sup>	0.166
F194		MS m/z 491.2 (M + 1) <sup>+</sup> .	0.126
F195		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.13 (s, 1 H), 9.53 (m, 1 H), 8.67 (s, 1H), 8.09 (d, J = 1.6 Hz, 1 H), 7.87 (d, J = 9.2 Hz, 1 H), 7.82 (dd, J = 1.6, 9.2 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1 H), 4.80 (s, 2H), 4.17 (q, J = 9.6 Hz, 2 H), 3.03 (m, 2 H), 2.38 (s, 3 H), 1.89 (m, 2 H). MS m/z 518.1 (M + 1) <sup>+</sup> .	0.15

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F196		MS m/z 444.7 (M + 1) <sup>+</sup> .	0.414
F197		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 9.95 (s, 1H), 9.33-9.31 (m, 1H), 8.53 (t, J = 5.6 Hz, 1H), 8.51 (s, 1H), 7.92 (d, J = 1.6 Hz, 1H), 7.69 (dd, J = 1.6, 8.0 Hz, 1H), 7.56 (s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.02 (dd, J = 1.6, 7.2 Hz, 1H), 3.51-3.46 (m, 4H), 3.27 (s, 3H), 2.42 (s, 3H), 2.33 (s, 3H). MS m/z 406.18 (M + 1) <sup>+</sup> .	0.11
F198			0.255
F199		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.22 (s, 1H), 9.53-9.51 (m, 1H), 8.72 (s, 1H), 8.13 (d, J = 1.6 Hz, 1H), 7.91-7.87 (m, 2H), 7.72-7.69 (m, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.40-7.25 (m, 2H), 2.39 (s, 3H). MS m/z 419.10 (M + 1) <sup>+</sup> .	0.126
F200		MS m/z 366.14 (M + 1) <sup>+</sup> .	0.12

TABLE 2-continued

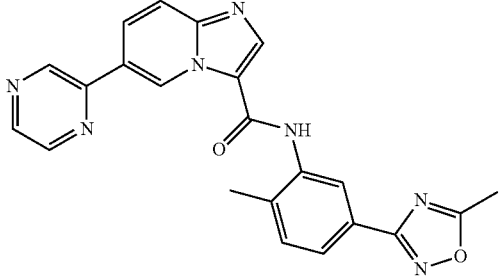
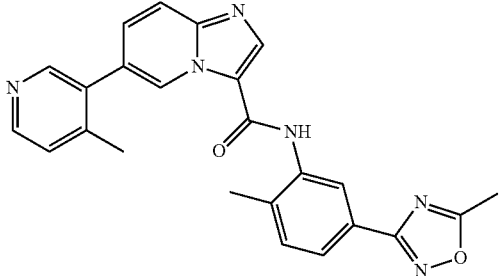
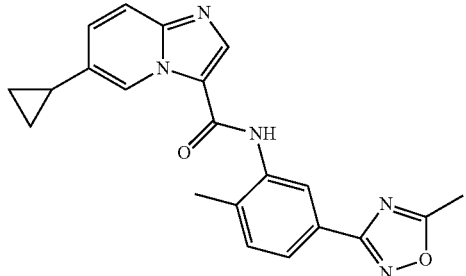
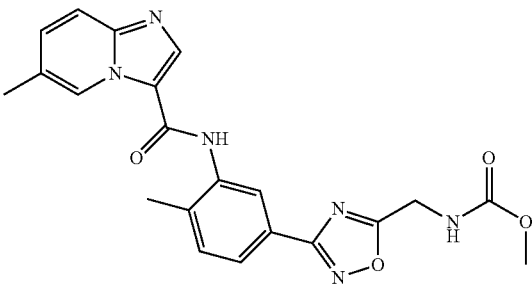
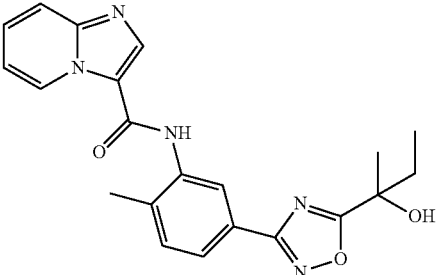
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F201		MS m/z 412.15 (M + 1) <sup>+</sup> .	0.125
F202		MS m/z 425.17 (M + 1) <sup>+</sup> .	0.135
F203		MS m/z 374.15 (M + 1) <sup>+</sup> .	0.144
F204		MS m/z 421.16 (M + 1) <sup>+</sup> .	0.157
F205		MS m/z 392.16 (M + 1) <sup>+</sup> .	0.174

TABLE 2-continued

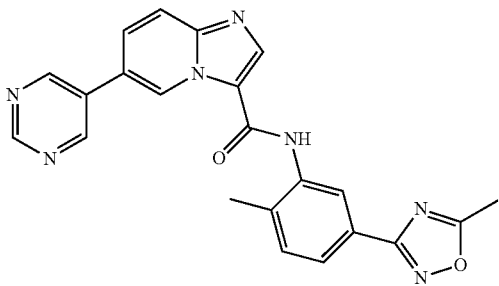
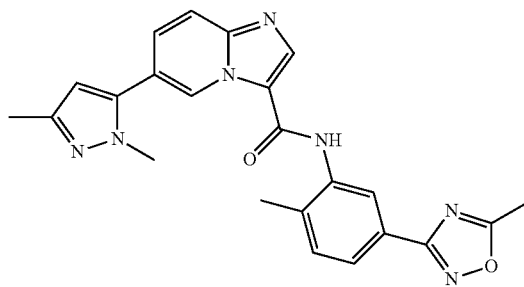
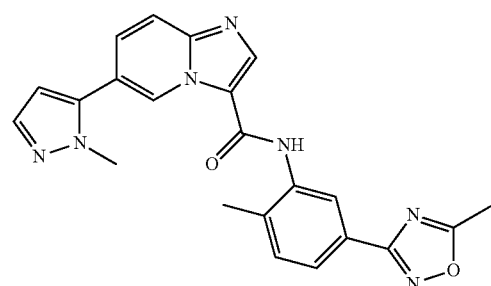
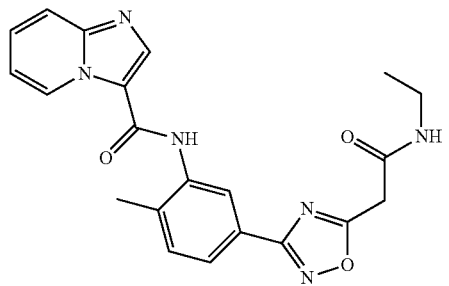
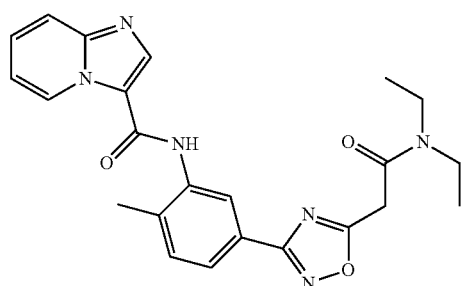
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F206		MS m/z 412.15 (M + 1) <sup>+</sup> .	0.196
F207		MS m/z 428.18 (M + 1) <sup>+</sup> .	0.223
F208		MS m/z 414.16 (M + 1) <sup>+</sup> .	0.228
F209		MS m/z 405.16 (M + 1) <sup>+</sup> .	0.318
F210		MS m/z 433.2 (M + 1) <sup>+</sup> .	0.431

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F211		MS m/z 446.23 (M + 1) <sup>+</sup> .	0.571
F212		MS m/z 447.21 (M + 1) <sup>+</sup> .	0.691
F213		MS m/z 405.17 (M + 1) <sup>+</sup> .	0.795
F214		MS m/z 517.22 (M + 1) <sup>+</sup> .	0.805
F215		MS m/z 422.17 (M + 1) <sup>+</sup> .	0.886



TABLE 2-continued

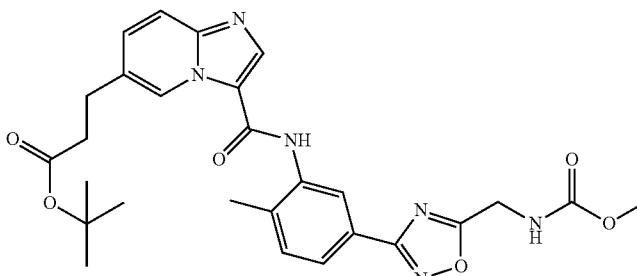
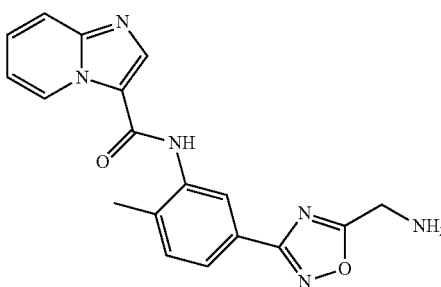
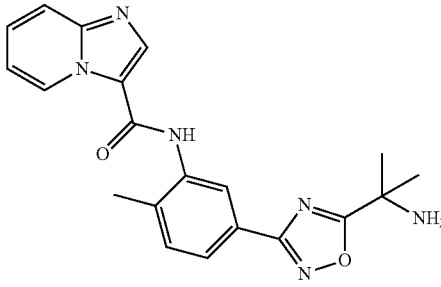
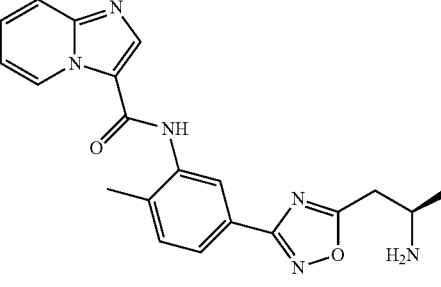
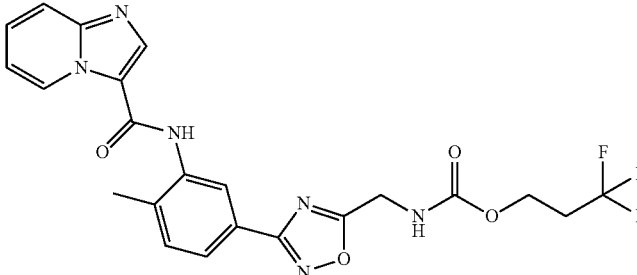
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F216		MS m/z 535.23 (M + 1) <sup>+</sup> .	1.026
F217		MS m/z 349.14 (M + 1) <sup>+</sup> .	1.033
F218		MS m/z 377.16 (M + 1) <sup>+</sup> .	1.059
F219		MS m/z 377.16 (M + 1) <sup>+</sup> .	1.186
F220		MS m/z 489.15 (M + 1) <sup>+</sup> .	1.189

TABLE 2-continued

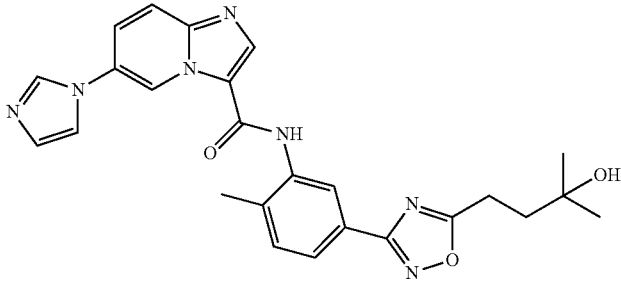
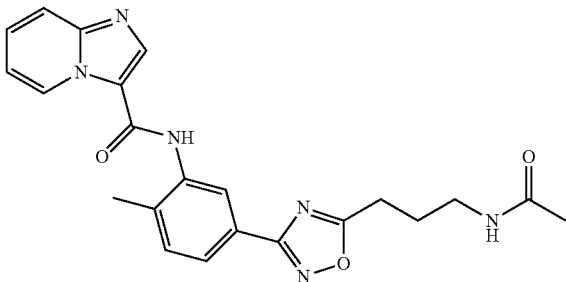
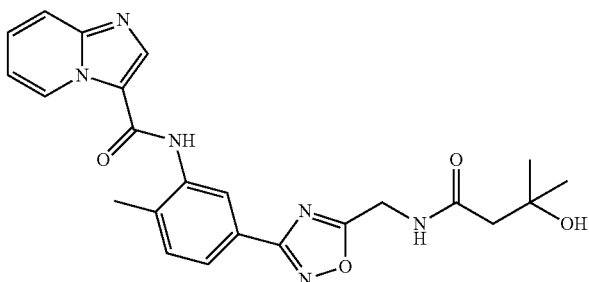
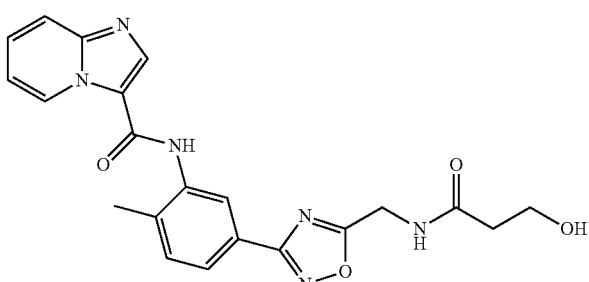
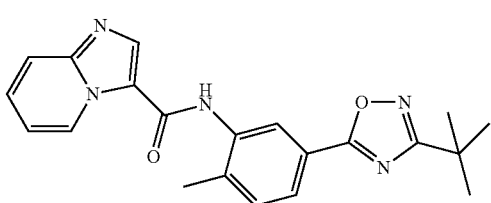
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F221		MS m/z 472.2 (M + 1) <sup>+</sup> .	1.247
F222		MS m/z 419.18 (M + 1) <sup>+</sup> .	1.317
F223		MS m/z 449.19 (M + 1) <sup>+</sup> .	1.461
F224		MS m/z 421.16 (M + 1) <sup>+</sup> .	1.479
F225		MS m/z 376.17 (M + 1) <sup>+</sup> .	1.59

TABLE 2-continued

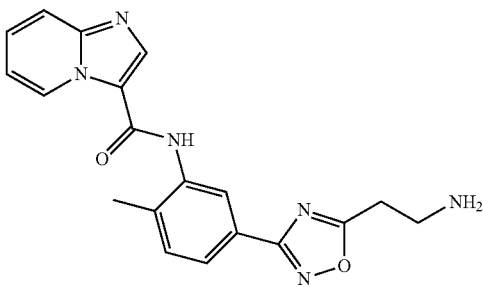
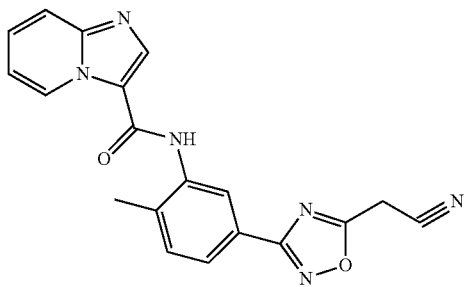
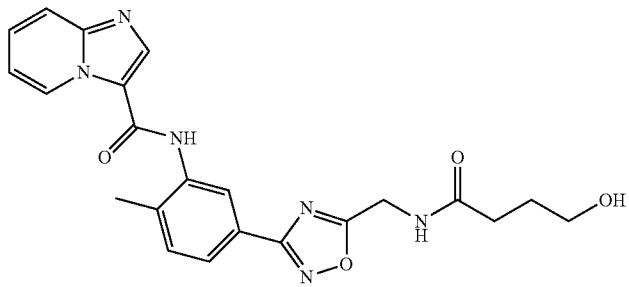
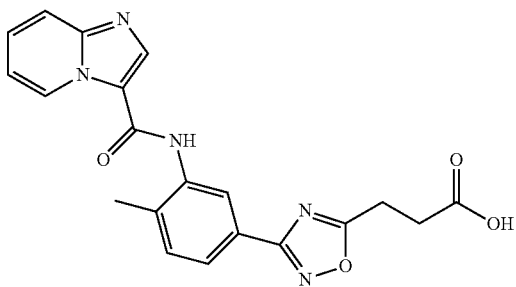
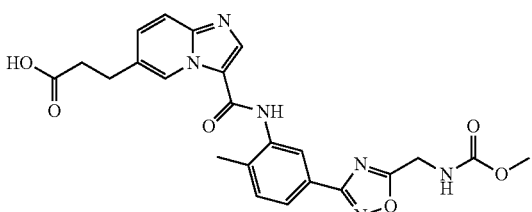
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F226		MS m/z 363.16 (M + 1) <sup>+</sup> .	2.181
F227		MS m/z 359.13 (M + 1) <sup>+</sup> .	2.38
F228		MS m/z 437.15 (M + 1) <sup>+</sup> .	2.486
F229		MS m/z 392.14 (M + 1) <sup>+</sup> .	5.45
F230		MS m/z 479.16 (M + 1) <sup>+</sup> .	>10

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F231		MS m/z 402.11 (M + 1) <sup>+</sup> .	>10
F232		MS m/z 479.17 (M + 1) <sup>+</sup> .	>10
F233		MS m/z 405.17 (M + 1) <sup>+</sup> .	>6*
F234		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.06 (s, 1H), 9.35 (s, 1H), 8.61 (s, 1H), 8.04 (d, J = 1.6 Hz, 1H), 7.84 (dd, J = 0.8, 9.2 Hz, 1H), 7.80 (dd, J = 1.6, 7.6 Hz, 1H), 7.51-7.48 (m, 2H), 4.90 (s, 2H), 2.66 (s, 3H), 2.35 (s, 3H), 2.20 (s, 3H), 2.17 (s, 3H), 1.44 (s, 9H). MS m/z 541.24 (M + 1) <sup>+</sup> .	0.209
F235		<sup>1</sup> H NMR (400 MHz, d <sub>6</sub> -DMSO) $\delta$ 10.20 (s, 1H), 9.39 (s, 1H), 8.72 (s, 1H), 8.04 (d, J = 2.0, 1H), 7.93 (d, J = 9.2 Hz, 1H), 7.82 (dd, J = 2.0, 8.0, 1H), 7.67 (dd, J = 2.0, 9.0, 1H), 7.50 (d, J = 8.0 Hz, 1H), 4.92 (s, 2H), 2.66 (s, 3H), 2.36 (s, 3H), 2.23 (s, 3H), 2.18 (s, 3H). MS m/z 485.18 (M + 1) <sup>+</sup> .	2.458

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F236		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.17 (s, 1H), 10.06 (s, 1H), 8.66 (s, 1H), 8.10 (d, $J = 2.0$ Hz, 1H), 7.97 (dd, $J = 2.0, 9.0$ Hz, 1H), 7.88 (dd, $J = 0.8, 9.0$ Hz, 1H), 7.82 (dd, $J = 2.0, 8.0$ Hz, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 5.07 (q, $J = 6.3$ Hz, 1H), 2.67 (s, 3H), 2.38 (s, 3H), 2.37 (s, 3H), 1.40 (d, $J = 6.3$ Hz, 3H). MS $m/z$ 474.15 ( $M + 1$ ) <sup>+</sup> .	0.166
F237		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.11 (s, 1H), 10.02 (s, 1H), 8.63 (s, 1H), 8.10 (d, $J = 1.6$ Hz, 1H), 7.92 (dd, $J = 1.8, 9.4$ Hz, 1H), 7.87 (dd, $J = 0.9, 9.4$ Hz, 1H), 7.82 (dd, $J = 1.7, 7.9$ Hz, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 2.67 (s, 3H), 2.40 (s, 3H), 2.38 (s, 3H), 2.34 (s, 3H). MS $m/z$ 444.14 ( $M + 1$ ) <sup>+</sup> .	0.182
F238		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.12 (s, 1H), 9.38 (s, 1H), 8.66 (s, 1H), 8.16 (s, 1H), 8.04 (s, 1H), 7.88 (d, $J = 9.3$ Hz, 1H), 7.81 (d, $J = 7.9$ Hz, 1H), 7.58 (s, 1H), 7.49 (d, $J = 8.1$ Hz, 1H), 4.74 (s, 2H), 3.42 (t, $J = 6.0$ Hz, 2H), 3.16 (d, $J = 5.8$ Hz, 2H), 2.66 (s, 3H), 2.35 (s, 3H), 2.23 (s, 3H), 2.17 (s, 3H). MS $m/z$ 528.22 ( $M + 1$ ) <sup>+</sup> .	0.31
F239		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.12 (s, 1H), 9.38 (s, 1H), 8.66 (s, 1H), 8.43-8.38 (m, 1H), 8.04 (s, 1H), 7.88 (d, $J = 9.3$ Hz, 1H), 7.81 (d, $J = 7.9$ Hz, 1H), 7.55 (d, $J = 9.3$ Hz, 1H), 7.49 (d, $J = 8.1$ Hz, 1H), 4.78 (s, 2H), 4.02-3.90 (m, 4H), 3.68-3.55 (m, 2H), 3.47 (s, 2H), 3.23-3.17 (m, 2H), 3.16-3.05 (m, 2H), 2.66 (s, 3H), 2.35 (s, 3H), 2.24 (s, 3H), 2.17 (s, 3H). MS $m/z$ 597.28 ( $M + 1$ ) <sup>+</sup> .	0.193

TABLE 2-continued

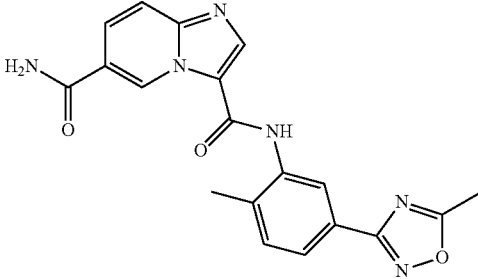
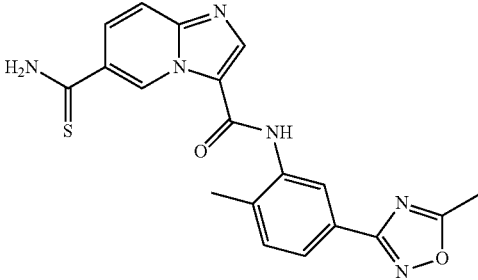
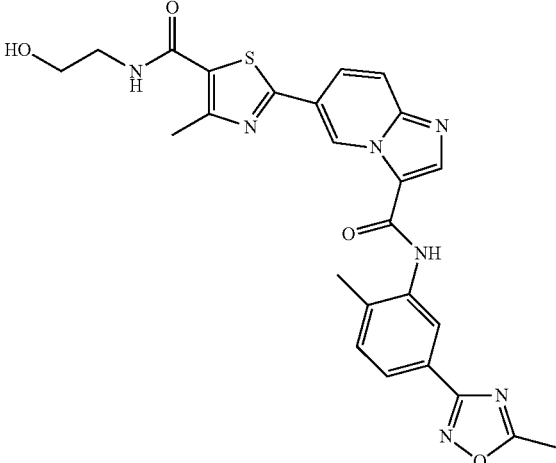
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F240		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.10 (s, 1H), 9.98 (dd, $J = 0.9, 1.7$ Hz, 1H), 8.64 (s, 1H), 8.25 (s, 1H), 8.11 (d, $J = 1.7$ Hz, 1H), 7.93 (dd, $J = 1.8, 9.4$ Hz, 1H), 7.85-7.79 (m, 2H), 7.63 (s, 1H), 7.50 (d, $J = 8.1$ Hz, 1H), 2.66 (s, 3H), 2.38 (s, 3H). MS $m/z$ 376.13 ( $M + 1$ ) <sup>+</sup> .	1.484
F241		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.12 (s, 1H), 10.11-10.10 (m, 1H), 10.09 (s, 1H), 9.79 (s, 1H), 8.65 (s, 1H), 8.10 (d, $J = 1.7$ Hz, 1H), 7.96 (dd, $J = 1.9, 9.5$ Hz, 1H), 7.83-7.76 (m, 2H), 7.50 (d, $J = 8.1$ Hz, 1H), 2.67 (s, 3H), 2.37 (s, 3H). MS $m/z$ 392.11 ( $M + 1$ ) <sup>+</sup> .	0.127
F242		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.16-10.15 (m, 2H), 8.67 (s, 1H), 8.27 (t, $J = 5.6$ Hz, 1H), 8.12 (d, $J = 1.7$ Hz, 1H), 7.98 (dd, $J = 1.9, 9.4$ Hz, 1H), 7.91 (dd, $J = 0.9, 9.4$ Hz, 1H), 7.82 (dd, $J = 1.8, 7.9$ Hz, 1H), 7.51 (d, $J = 8.1$ Hz, 1H), 3.50 (t, $J = 6.2$ Hz, 2H), 3.33-3.28 (m, 3H), 2.67 (s, 3H), 2.63 (s, 3H), 2.39 (s, 3H). MS $m/z$ 517.15 ( $M + 1$ ) <sup>+</sup> .	0.155

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F243		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.17 (s, 1H), 10.16 (s, 1H), 8.68 (s, 1H), 8.36-8.27 (m, 1H), 8.10 (s, 1H), 7.97 (s, 1H), 7.94 (s, 1H), 7.84-7.80 (m, 1H), 7.52 (s, 1H), 3.95-3.69 (m, 8H), 3.47-3.38 (m, 4H), 2.77 (s, 3H), 2.67 (s, 3H), 2.66 (s, 3H), 2.38 (s, 3H). MS $m/z$ 599.24 ( $M + 1$ ) <sup>+</sup> .	0.194
F244		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.17 (s, 1H), 10.16 (s, 1H), 8.68 (s, 1H), 8.43-8.38 (m, 1H), 8.11 (s, 1H), 7.98 (dd, $J = 1.8, 9.4$ Hz, 1H), 7.93 (d, $J = 9.4$ Hz, 1H), 7.85-7.81 (m, 1H), 7.51 (d, $J = 8.1$ Hz, 1H), 4.41-3.76 (m, 8H), 3.53-3.35 (m, 2H), 3.31-3.26 (m, 2H), 2.75 (s, 3H), 2.67 (s, 3H), 2.65 (s, 3H), 2.38 (s, 3H), 1.86-1.75 (m, 2H). MS $m/z$ 599.24 ( $M + 1$ ) <sup>+</sup> .	0.185

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F245		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.19-10.18 (m, 1H), 10.17 (s, 1H), 8.68 (s, 1H), 8.51 (s, 1H), 8.12 (s, 1H), 7.99 (dd, $J = 1.9, 9.4$ Hz, 1H), 7.93 (d, $J = 9.4$ Hz, 1H), 7.84-7.78 (m, 1H), 7.51 (d, $J = 8.1$ Hz, 1H), 3.99 (s, 2H), 3.69-3.50 (m, 8H), 3.18-3.05 (m, 2H), 2.68 (s, 3H), 2.67 (s, 3H), 2.39 (s, 3H). MS $m/z$ 586.21 ( $M + 1$ ) $^+$ .	0.12
F246		MS $m/z$ 421.1 ( $M + 1$ ) $^+$ .	1.801
F247		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.11 (s, 1H), 9.59 (s, 1H), 8.63 (s, 1H), 8.05 (s, 1H), 7.86 (d, $J = 9.4$ , 1H), 7.81 (dd, $J = 1.7, 7.9$ Hz, 1H), 7.63 (dd, $J = 1.8, 9.3$ Hz, 1H), 7.49 (d, $J = 8.0$ Hz, 1H), 2.66 (s, 3H), 2.43 (s, 3H), 2.36 (s, 3H). MS $m/z$ 474.11 ( $M + 1$ ) $^+$ .	0.341



TABLE 2-continued

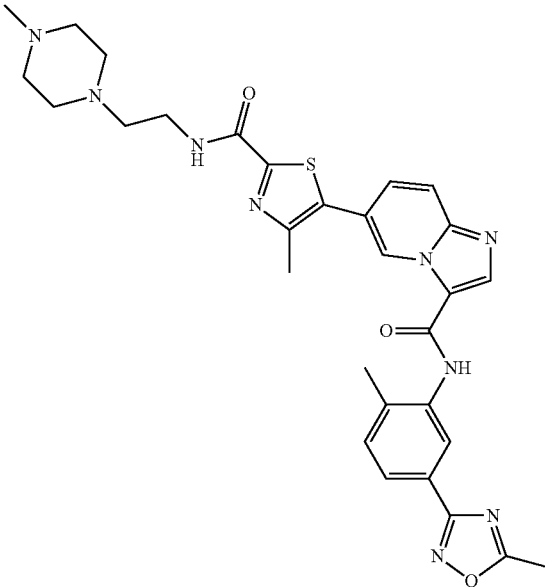
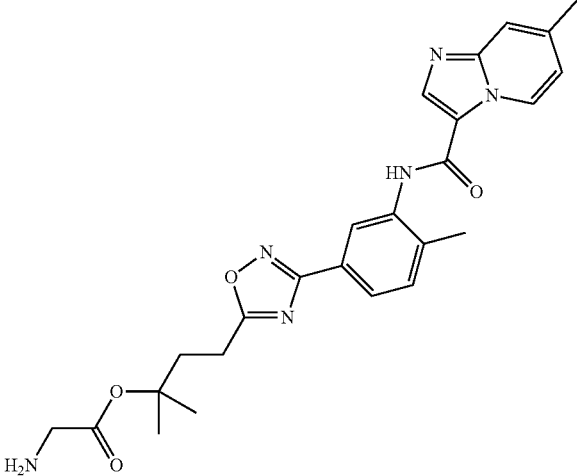
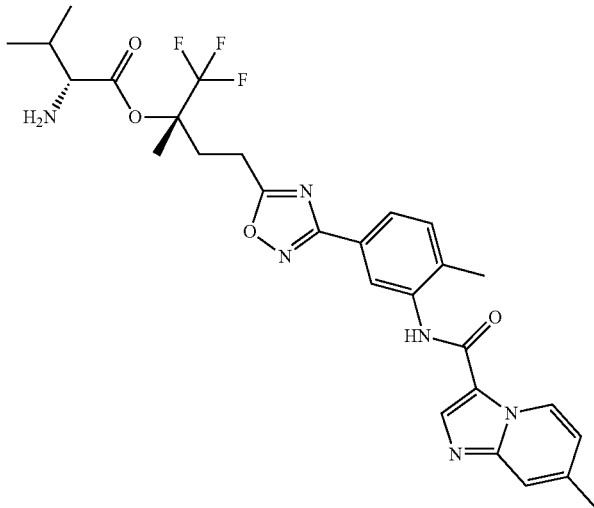
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu$ M
F248		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.17 (s, 1H), 9.67 (s, 1H), 8.94-8.88 (m, 1H), 8.68 (s, 1H), 8.04 (s, 1H), 7.94 (d, $J = 9.3$ Hz, 1H), 7.83-7.79 (m, 1H), 7.71 (dd, $J = 1.9, 9.3$ Hz, 1H), 7.50 (d, $J = 8.1$ Hz, 1H), 4.60-4.11 (m, 8H), 3.51-3.42 (m, 3H), 2.77 (s, 4H), 2.66 (s, 3H), 2.54 (d, $J = 5.4$ Hz, 2H), 2.36 (s, 4H). MS $m/z$ 599.24 ( $M + 1$ ) $^+$ .	0.14
F249		MS $m/z$ 477.2 ( $M + 1$ ) $^+$ .	0.108

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F250		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.12 (s, 1H), 9.38 (d, $J = 7.1$ Hz, 1H), 8.64 (s, 1H), 8.07 (s, 1H), 7.83 (d, $J = 7.9$ Hz, 1H), 7.67 (s, 1H), 7.50 (d, $J = 8.2$ Hz, 1H), 7.19 (s, 1H), 3.72 (d, $J = 4.2$ Hz, 3H), 3.69 (d, $J = 4.2$ Hz, 3H), 3.36-3.31 (m, 1H), 3.23 (s, 2H), 2.48 (s, 3H), 2.36 (s, 3H), 1.73 (s, 3H), 1.50 (s, 1H). MS $m/z$ 567.15 ( $M + 1$ ) <sup>+</sup> .	5.48
F251		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.71 (s, 1H), 9.51 (d, $J = 7.1$ Hz, 1H), 9.14 (s, 1H), 8.05 (s, 1H), 7.88 (s, 1H), 7.84 (dd, $J = 2.0, 8.0$ Hz, 1H), 7.52 (d, $J = 8.2$ Hz, 1H), 7.43 (d, $J = 7.2$ Hz, 1H), 6.70 (s, 2H), 4.53-4.48 (m, 2H), 4.14-4.11 (m, 1H), 3.82-3.76 (m, 2H), 3.27-3.22 (m, 1H), 2.56 (s, 3H), 2.39 (s, 3H), 1.81 (s, 3H), 1.01 (d, $J = 7.2$ Hz, 3H), 0.97 (d, $J = 6.8$ Hz, 3H). MS $m/z$ 572.24 ( $M + 1$ ) <sup>+</sup> .	0.142

TABLE 2-continued

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) $\mu\text{M}$
F252		$^1\text{H NMR}$ (400 MHz, $d_6$ -DMSO) $\delta$ 10.68 (s, 1H), 9.50 (d, $J = 7.2$ Hz, 1H), 9.12 (s, 1H), 8.05 (d, $J = 1.6$ Hz, 1H), 7.86-7.84 (m, 2H), 7.52 (d, $J = 8.0$ Hz, 1H), 7.41 (d, $J = 7.2$ Hz, 1H), 6.70 (s, 2H), 4.15-4.11 (m, 2H), 3.97-3.95 (m, 1H), 3.27-3.22 (m, 2H), 2.80-2.77 (m, 1H), 2.56 (s, 3H), 2.39 (s, 3H), 1.78 (s, 3H), 1.01 (d, $J = 6.8$ Hz, 3H), 0.99 (d, $J = 6.8$ Hz, 3H). MS $m/z$ 572.24 ( $M + 1$ ) <sup>+</sup> .	0.134

\*20% FBS instead of 1% FBS

#### Assays

**[0669]** Compounds of Formula (I) and Formula (II) provided herein were assayed to measure their capacity to inhibit c-kit and PDGFR kinases using the appropriate assay described below: c-Kit inhibition was evaluated using the Mo7e cell proliferation assay, and PDGFR inhibition was evaluated using the Rat A10 cell proliferation assay and the Human TGHA-VSMC cell proliferation assay.

#### Mo7e Cell Proliferation Assay

**[0670]** The compounds of Table 1 and Table 2 were tested for inhibition of SCF dependent proliferation using human Mo7e cells which endogenously express c-kit in a 384 well format. Three-fold serially diluted test compounds ( $C_{\text{max}}=10$  mM) were evaluated for their antiproliferative activity of Mo7e cells stimulated with human recombinant SCF. After 48 hours of incubation at 37° C., cell viability was measured by adding 25  $\mu\text{L}$  of CellTiter Glo (Promega) to the cells and the luminescence was measured by a CLIPR CCD camera (Molecular Devices).

#### Rat A10 Cell Proliferation Assay

**[0671]** Rat A10 cells (ATCC) were resuspended in DMEM supplemented with 1% FBS or 20% FBS and 10 ng/mL recombinant rat PDGF-BB at 20,000 cells/mL. The cells were aliquoted into 384 well plates at 50  $\mu\text{L}$ /well and incubated for 4 hours at 37° C. 0.5  $\mu\text{L}$  of test compound 3-fold serially diluted in DMSO was added to each well. The plates were returned to the incubator for a further 68 hours. 25  $\mu\text{L}$  of CellTiter-Glo (Promega) was added to each well and the plates were incubated on the bench for 15 minutes. Luminescence was then read using a CLIPR CCD camera (Molecular Devices).

#### Human TGHA-VSMC Cell Proliferation Assay

**[0672]** Human TGHA-VSMC cells (ATCC) were resuspended in DMEM supplemented with 1% FBS and 30 ng/mL

recombinant human PDGF-BB at 60,000 cells/mL. The cells were aliquoted into 384 well plates at 50  $\mu\text{L}$ /well and incubated for 4 hours at 37° C. 0.5  $\mu\text{L}$  of test compound 3-fold serially diluted in DMSO was added to each well. The plates were returned to the incubator for a further 68 hours. 25  $\mu\text{L}$  of CellTiter-Glo (Promega) was added to each well and the plates were incubated on the bench for 15 minutes. Luminescence was then read using a CLIPR CCD camera (Molecular Devices).

#### Certain Assay Results

**[0673]** Various compounds of Formula (I) and Formula (II) in free form or in pharmaceutically acceptable salt form, exhibit pharmacological properties, for example, as indicated by the tests described herein and presented in Table 1 and Table 2. The  $\text{IC}_{50}$  value is given as that concentration of the test compound in question that provoke a response halfway between the baseline and maximum responses. Certain compounds of Formula (I) or Formula (II) having specific  $\text{IC}_{50}$  for c-kit inhibition values of less than or equal to 100 nM are listed in Table 1, while certain compounds of Formula (I) or Formula (II) having specific  $\text{IC}_{50}$  for c-kit inhibition values greater than 100 nM are listed in Table 2.

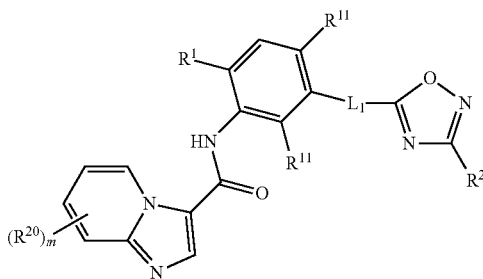
**[0674]** In other embodiments, compounds of Formula (I) or Formula (II) have  $\text{IC}_{50}$  values for c-kit inhibition in the range from 1 nM to 1  $\mu\text{M}$ . In other embodiments, compounds of Formula (I) or Formula (II) have  $\text{IC}_{50}$  values for c-kit inhibition in the range from 1 nM to 500 nM. In other embodiments, compounds of Formula (I) or Formula (II) have  $\text{IC}_{50}$  values for c-kit inhibition in the range from 1 nM to 200 nM. In other embodiments, compounds of Formula (I) or Formula (II) have  $\text{IC}_{50}$  values for c-kit inhibition in the range from 1 nM to 100 nM. In other embodiments, compounds of Formula (I) or Formula (II) have  $\text{IC}_{50}$  values for c-kit inhibition in the range from 1 nM to 50 nM. In other embodiments, compounds of Formula (I) or Formula (II) have  $\text{IC}_{50}$  values for c-kit inhibi-

tion in the range from 1 nM to 25 nM. In other embodiments, compounds of Formula (I) or Formula (II) have IC<sub>50</sub> values for c-kit inhibition in the range from 1 nM to 10 nM. In other embodiments, compounds of Formula (I) or Formula (II) have IC<sub>50</sub> values for c-kit inhibition in the range from 1 nM to 5 nM. In other embodiments, compounds of Formula (I) or Formula (II) have IC<sub>50</sub> values for c-kit inhibition in the range from 1 nM to 2.5 nM.

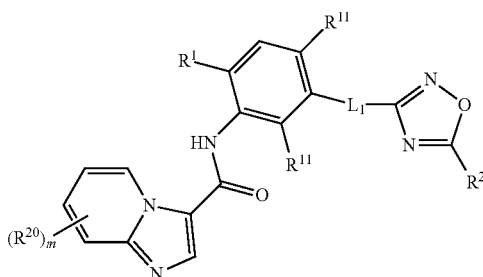
**[0675]** It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims.

1. A compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof:

Formula (I)



Formula (II)



wherein:

m is 1 and R<sup>20</sup> is selected from H, halo, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>haloalkoxy, deuterium, deuterated C<sub>1</sub>-C<sub>6</sub>alkyl, —CN, —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —C(O)R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>C(=O)OR<sup>4</sup>, R<sup>8</sup>, —(CR<sup>9</sup>)<sub>n</sub>R<sup>8</sup>, —((CR<sup>9</sup>)<sub>n</sub>O)<sub>n</sub>R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>C(=O)R<sup>4</sup>, —C(=O)N(R<sup>4</sup>)<sub>2</sub>, —N(R<sup>4</sup>)<sub>2</sub>, —C(=S)N(R<sup>4</sup>)<sub>2</sub>, —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —OW and —(CR<sup>9</sup>)<sub>n</sub>CN, or m is 4 and R<sup>20</sup> is deuterium;

R<sup>1</sup> is selected from C<sub>1</sub>-C<sub>6</sub>alkyl and halo;

each R<sup>11</sup> is independently selected from H, halo and C<sub>1</sub>-C<sub>6</sub>alkyl;

L<sub>1</sub> is a bond, —NH— or —C(O)NH—;

R<sup>2</sup> is selected from C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl, —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>S(=O)<sub>2</sub>NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>CN, —(CR<sup>9</sup>)<sub>n</sub>C(=O)R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>OC(=O)R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>C(=O)OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>C(=O)NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>OC(=O)NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>OC(=O)NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>OCR<sup>9</sup>R<sup>6</sup>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>

—(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>CR<sup>5</sup>R<sup>6</sup>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>CR<sup>9</sup>R<sup>6</sup>OC(O)(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>OC(O)(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>, —CR<sup>9</sup>R<sup>5</sup>R<sup>6</sup>, —CR<sup>9</sup>R<sup>9</sup>R<sup>5</sup>, —CR<sup>9</sup>R<sup>6</sup>NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>, —NR<sup>4</sup>(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —NR<sup>4</sup>(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —NR<sup>4</sup>(CR<sup>9</sup>)<sub>n</sub>R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)NR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>S(=O)<sub>2</sub>R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —CR<sup>9</sup>R<sup>5</sup>NR<sup>4</sup>S(=O)<sub>2</sub>R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>5</sup>C(=O)R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)O(CR<sup>9</sup>)<sub>n</sub>R<sup>11</sup>, —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, and —(CR<sup>9</sup>)<sub>n</sub>NR<sup>4</sup>C(=O)O(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>;

each R<sup>4</sup> is independently selected from H and C<sub>1</sub>-C<sub>6</sub>alkyl;

each R<sup>5</sup> is independently selected from —NHC(O)OR<sup>4</sup>, —OP(O)(OR<sup>4</sup>)<sub>2</sub> and —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>;

each R<sup>6</sup> is a C<sub>1</sub>-C<sub>6</sub>haloalkyl;

each R<sup>9</sup> is independently selected from H and C<sub>1</sub>-C<sub>6</sub>alkyl;

R<sup>8</sup> is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl and substituted 4-6 membered heterocycloalkyl of R<sup>8</sup> are substituted with 1-3 substituents independently selected from C<sub>1</sub>-C<sub>6</sub>alkyl, halo, —(C(R<sup>9</sup>)<sub>2</sub>)<sub>n</sub>OR<sup>4</sup>, —C(O)NR<sup>4</sup>, —NR<sup>4</sup>, —R<sup>10</sup>, —(C(R<sup>9</sup>)<sub>2</sub>)<sub>n</sub>R<sup>19</sup>, —(C(R<sup>9</sup>)<sub>2</sub>)<sub>n</sub>C(O)OR<sup>4</sup>, —C(O)OR<sup>4</sup>, —(C(R<sup>9</sup>)<sub>2</sub>)<sub>n</sub>C(O)NR<sup>4</sup>, —C(O)NR<sup>4</sup>(C(R<sup>9</sup>)<sub>2</sub>)<sub>n</sub>R<sup>19</sup>, —(C(R<sup>9</sup>)<sub>2</sub>)<sub>n</sub>C(O)NR<sup>4</sup>(C(R<sup>9</sup>)<sub>2</sub>)<sub>n</sub>R<sup>19</sup>, —(C(R<sup>9</sup>)<sub>2</sub>)<sub>n</sub>C(O)NR<sup>4</sup>(C(R<sup>9</sup>)<sub>2</sub>)<sub>n</sub>OR<sup>4</sup>, —C(O)NR<sup>4</sup>(C(R<sup>9</sup>)<sub>2</sub>)<sub>n</sub>OR<sup>4</sup>, —C(O)OR<sup>4</sup>, —C(O)OR<sup>4</sup> and —S(O)<sub>2</sub>R<sup>4</sup>;

R<sup>10</sup> is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, and a substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl and substituted 4-6 membered heterocycloalkyl of R<sup>10</sup> are substituted with 1-3 substituents independently selected from C<sub>1</sub>-C<sub>6</sub>alkyl, and  $-(C(R^9)_2)_nOR^4$ ;

t is 1, 2 or 3, and

each n is independently selected from 1, 2, 3 and 4.

2. The compound of claim 1 wherein:

m is 1 and R<sup>20</sup> is selected from H, halo, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>1</sub>-C<sub>6</sub>haloalkoxy, deuterium, deuterated C<sub>1</sub>-C<sub>6</sub>alkyl,  $-\text{CN}$ ,  $-(CR^9_2)_nOR^4$ ,  $-(C(O)R^4)_n$ ,  $-(CR^9_2)_nC(=O)OR^4$ , R<sup>8</sup>,  $-(CR^9_2)_nR^8$ ,  $-(CR^9_2)_nO$ , R<sup>4</sup>,  $-(CR^9_2)_nO(CR^9_2)_nR^6$ ,  $-(CR^9_2)_nC(=O)R^4$ ,  $-(C(=O)N(R^4))_2$ ,  $-(CR^9_2)_nOR^4$ ,  $-OR^4$  and  $-(CR^9_2)_nCN$ ,

or m is 4 and R<sup>20</sup> is deuterium;

R<sup>1</sup> is selected from C<sub>1</sub>-C<sub>6</sub>alkyl and halo;

each R<sup>11</sup> is independently selected from H, halo and C<sub>1</sub>-C<sub>6</sub>alkyl;

L<sub>1</sub> is a bond,  $-\text{NH}-$  or  $-\text{C(O)NH}-$ ;

R<sup>2</sup> is selected from C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl,  $-(CR^9_2)_nOR^4$ ,  $-(CR^9_2)_nR^6$ ,  $-(CR^9_2)_nS(=O)_2NR^4$ ,  $-(CR^9_2)_nCN$ ,  $-(CR^9_2)_nC(=O)R^4$ ,  $-(CR^9_2)_nOC(=O)R^4$ ,  $-(CR^9_2)_nC(=O)OR^4$ ,  $-(CR^9_2)_nC(=O)NR^4$ ,  $-(CR^9_2)_nO(CR^9_2)_nOR^4$ ,  $-(CR^9_2)_nO(CR^9_2)_nO(CR^9_2)_nR^6$ ,  $-(CR^9_2)_nOCR^9R^6R^6$ ,  $-(CR^9_2)_nCR^9R^6R^6$ ,  $-(CR^9_2)_nCR^9R^6R^6$ ,  $-(CR^9_2)_nNR^4$ ,  $-(CR^9_2)_nNR^4$ ,  $-(CR^9_2)_nNR^4C(=O)R^4$ ,  $-(CR^9_2)_nNR^4C(=O)OR^4$ ,  $-(CR^9_2)_nNR^4C(=O)NR^4$ ,  $-(CR^9_2)_nNR^4C(=O)R^4$ ,  $-(CR^9_2)_nNR^4C(=O)O(CR^9_2)_nOR^4$ ,  $-(CR^9_2)_nNR^4C(=O)(CR^9_2)_nOR^4$ ,  $-(CR^9_2)_nNR^4C(=O)R^6$ ,  $-(CR^9_2)_nNR^4C(=O)(CR^9_2)_nR^6$ ,  $-(CR^9_2)_nNR^4C(=O)O(CR^9_2)_nR^{11}$ ,  $-(CR^9_2)_nNR^4C(=O)(CR^9_2)_nO(CR^9_2)_nR^6$ , and  $-(CR^9_2)_nNR^4C(=O)O(CR^9_2)_nR^6$ ;

each R<sup>4</sup> is independently selected from H and C<sub>1</sub>-C<sub>6</sub>alkyl;

each R<sup>5</sup> is independently selected from  $-\text{NHC(O)OR}^4$ ,  $-OR^4$  and  $-(CR^9_2)_nOR^4$ ;

each R<sup>6</sup> is a C<sub>1</sub>-C<sub>6</sub>haloalkyl;

each R<sup>9</sup> is independently selected from H and C<sub>1</sub>-C<sub>6</sub>alkyl;

R<sup>8</sup> is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, an oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered

heteroaryl with 1-4 heteroatoms selected from N, substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl and substituted 4-6 membered heterocycloalkyl of R<sup>8</sup> are substituted with 1-3 substituents independently selected from C<sub>1</sub>-C<sub>6</sub>alkyl, halo,  $-(C(R^9)_2)_nOR^4$ ,  $-(C(O)NR^4)_2$ ,  $-R^{10}$ ,  $-(C(R^9)_2)_nR^{10}$ ,  $-OR^4$ ,  $-(C(R^9)_2)_nC(O)OR^4$  and  $-S(O)_2R^4$ ;

R<sup>10</sup> is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, and a substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl,

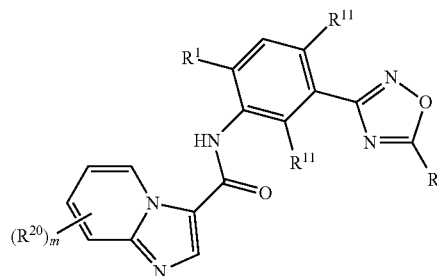
wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C<sub>3</sub>-C<sub>8</sub>cycloalkyl and substituted 4-6 membered heterocycloalkyl of R<sup>10</sup> are substituted with 1-3 substituents independently selected from C<sub>1</sub>-C<sub>6</sub>alkyl, and  $-(C(R^9)_2)_nOR^4$ ;

t is 1, 2 or 3, and

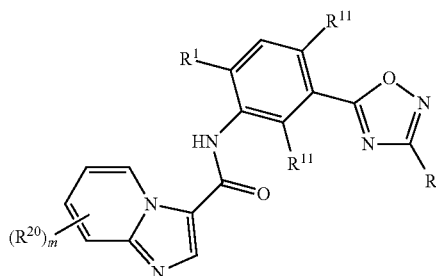
each n is independently selected from 1, 2, 3 and 4.

3. The compound of claim 1, wherein the compound is a compound of Formula (Ia), Formula (IIa), Formula (Ib) or Formula (IIb):

Formula (Ia)

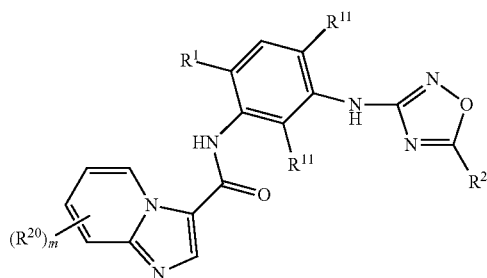


Formula (IIa)

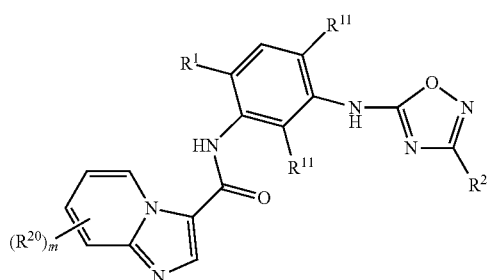


-continued

Formula (Ib)



Formula (IIb)



wherein:

$m$  is 1 and  $R^{20}$  is selected from H, halo,  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ haloalkyl,  $C_1$ - $C_6$ haloalkoxy, deuterium, deuterated  $C_1$ - $C_6$ alkyl,  $-\text{CN}$ ,  $-(\text{CR}^9)_n\text{OR}^4$ ,  $-\text{C}(\text{O})\text{R}^4$ ,  $-(\text{CR}^9)_2\text{C}(\text{O})\text{OR}^4$ ,  $\text{R}^8$ ,  $-(\text{CR}^9)_2\text{R}^8$ ,  $-(\text{CR}^9)_2\text{O}\text{R}^4$ ,  $-(\text{CR}^9)_2\text{O}(\text{CR}^9)_n\text{R}^6$ ,  $-(\text{CR}^9)_2\text{C}(\text{O})\text{R}^4$ ,  $-\text{C}(\text{O})\text{N}(\text{R}^4)_2$ ,  $-(\text{CR}^9)_2\text{OR}^4$ ,  $-\text{OR}^4$  and  $-(\text{CR}^9)_2\text{CN}$ ;

or  $m$  is 4 and  $R^{20}$  is deuterium;

$R^1$  is selected from  $C_1$ - $C_6$ alkyl and halo;

each  $R^{11}$  is independently selected from H, halo and  $C_1$ - $C_6$ alkyl;

$R^2$  is selected from  $C_1$ - $C_6$ alkyl,  $C_1$ - $C_6$ haloalkyl,  $C_2$ - $C_8$ alkenyl,  $-(\text{CR}^9)_2\text{OR}^4$ ,  $-(\text{CR}^9)_2\text{R}^6$ ,  $-(\text{CR}^9)_2\text{S}(\text{O})_2\text{NR}^4$ ,  $-(\text{CR}^9)_2\text{CN}$ ,  $-(\text{CR}^9)_2\text{C}(\text{O})\text{R}^4$ ,  $-(\text{CR}^9)_2\text{OC}(\text{O})\text{R}^4$ ,  $-(\text{CR}^9)_2\text{C}(\text{O})\text{OR}^4$ ,  $-(\text{CR}^9)_2\text{C}(\text{O})\text{NR}^4$ ,  $-(\text{CR}^9)_2\text{OC}(\text{O})\text{NR}^4$ ,  $-(\text{CR}^9)_2\text{O}(\text{CR}^9)_n\text{OR}^4$ ,  $-(\text{CR}^9)_2\text{O}(\text{CR}^9)_n\text{R}^6$ ,  $-(\text{CR}^9)_2\text{O}(\text{CR}^9)_n\text{O}(\text{CR}^9)_n\text{R}^6$ ,  $-(\text{CR}^9)_2\text{OCR}^9\text{R}^6$ ,  $-(\text{CR}^9)_2\text{CR}^9\text{R}^5\text{R}^6$ ,  $-(\text{CR}^9)_2\text{CR}^5\text{R}^6\text{R}^6$ ,  $-\text{CR}^9\text{R}^5\text{R}^6$ ,  $-\text{CR}^9\text{R}^9\text{R}^5$ ,  $-\text{CR}^9\text{R}^6\text{NR}^4$ ,  $-(\text{CR}^9)_2\text{NR}^4$ ,  $-\text{NR}^4(\text{CR}^9)_2\text{OR}^4$ ,  $-\text{NR}^4(\text{CR}^9)_n\text{R}^6$ ,  $-\text{NR}^4(\text{CR}^9)_2\text{R}^4$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{R}^4$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{OR}^4$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{R}^6$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{S}(\text{O})_2\text{R}^4$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{O}(\text{CR}^9)_n\text{OR}^4$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{O}(\text{CR}^9)_n\text{R}^6$ ,  $-(\text{CR}^9)_2\text{NR}^5\text{C}(\text{O})\text{R}^6$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{O}(\text{CR}^9)_n\text{R}^{11}$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{O}(\text{CR}^9)_n\text{R}^6$ , and  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{O}(\text{CR}^9)_n\text{R}^6$ ;

each  $R^4$  is independently selected from H and  $C_1$ - $C_6$ alkyl;

each  $R^5$  is independently selected from  $-\text{NHC}(\text{O})\text{OR}^4$ ,  $-\text{OR}^4$  and  $-(\text{CR}^9)_2\text{OR}^4$ ;

each  $R^6$  is a  $C_1$ - $C_6$ haloalkyl;

each  $R^9$  is independently selected from H and  $C_1$ - $C_6$ alkyl;

$R^8$  is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, O or S, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted  $C_3$ - $C_8$ cycloalkyl, an oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted  $C_3$ - $C_8$ cycloalkyl and substituted 4-6 membered heterocycloalkyl of  $R^8$  are substituted with 1-3 substituents independently selected from  $C_1$ - $C_6$ alkyl, halo,  $-(\text{C}(\text{R}^9)_2)_n\text{OR}^4$ ,  $-\text{C}(\text{O})\text{NR}^4_2-\text{NR}^4_2$ ,  $-\text{R}^{10}$ ,  $-(\text{C}(\text{R}^9)_2)_n\text{R}^{10}$ ,  $-(\text{C}(\text{R}^9)_2)_n\text{C}(\text{O})\text{OR}^4$  and  $-\text{S}(\text{O})_2\text{R}^4$ ;

$R^{10}$  is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted  $C_3$ - $C_8$ cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, and a substituted  $C_3$ - $C_8$ cycloalkyl,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted  $C_3$ - $C_8$ cycloalkyl and substituted 4-6 membered heterocycloalkyl of  $R^{10}$  are substituted with 1-3 substituents independently selected from  $C_1$ - $C_6$ alkyl, and  $-(\text{C}(\text{R}^9)_2)_n\text{OR}^4$ ;

$t$  is 1, 2 or 3, and

each  $n$  is independently selected from 1, 2, 3 and 4.

4. The compound of claim 1 wherein  $R^1$  is selected from  $-\text{CH}_3$  and F.

5. The compound of claim 1, wherein  $R^1$  is  $-\text{CH}_3$ .

6. The compound of claim 1, wherein each  $R^{11}$  is independently selected from H, F and  $-\text{CH}_3$ .

7. The compound of claim 1, wherein each  $R^{11}$  is H.

8. The compound of claim 1, wherein:

$R^2$  is selected from  $-(\text{CR}^9)_2\text{CN}$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{OR}^4$ ,  $-(\text{CR}^9)_2\text{OR}^4$ ,  $-(\text{CR}^9)_2\text{C}(\text{O})\text{NR}^4_2$ ,  $-(\text{CR}^9)_2\text{C}(\text{O})\text{R}^4$ ,  $C_1$ - $C_6$ alkyl,  $C_2$ - $C_8$ alkenyl,  $-(\text{CR}^9)_2\text{CR}^5\text{R}^6\text{R}^6$ ,  $-\text{CR}^5\text{R}^5\text{NR}^4\text{S}(\text{O})_2\text{R}^4$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{S}(\text{O})_2\text{R}^4$ ,  $-(\text{CR}^9)_2\text{NR}^4\text{C}(\text{O})\text{R}^6$ ,  $-(\text{CR}^9)_2\text{O}(\text{CR}^9)_n\text{OR}^4$ ,  $-(\text{CR}^9)_2\text{C}(\text{O})\text{OR}^4$ ,

- (CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>CR<sup>9</sup>R<sup>5</sup>R<sup>6</sup>, —NR<sup>4</sup>(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —NR<sup>4</sup>(CR<sup>9</sup>)<sub>n</sub>R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup> and —(CR<sup>9</sup>)<sub>n</sub>OCR<sup>9</sup>R<sup>6</sup>R<sup>6</sup>.
9. The compound of claim 1, wherein:  
R<sup>2</sup> is selected from —(CR<sup>9</sup>)<sub>n</sub>CR<sup>9</sup>R<sup>5</sup>R<sup>6</sup> and —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>.
10. The compound of claim 1, wherein each R<sup>4</sup> is independently selected from H, methyl, ethyl, propyl, butyl, i-propyl and t-butyl.
11. The compound of claim 1, wherein each R<sup>5</sup> is independently selected from, —OR<sup>4</sup> and —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>.
12. The compound of claim 1, wherein each R<sup>5</sup> is independently selected from OH and —CH<sub>2</sub>OH.
13. The compound of claim 1, wherein each R<sup>6</sup> is independently selected from —CH<sub>2</sub>F, —CHF<sub>2</sub>, —CH<sub>2</sub>CHF<sub>2</sub>, —CH<sub>2</sub>CF<sub>3</sub> and —CF<sub>3</sub>.
14. The compound of claim 1, wherein each R<sup>9</sup> is independently selected from H, methyl and ethyl.
15. (canceled)
16. The compound of claim 1, wherein R<sup>2</sup> is —C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>OH or —CH<sub>2</sub>CH<sub>2</sub>C(CH<sub>3</sub>)OHCF<sub>3</sub>.
17. The compound of claim 1 wherein m is 1 and R<sup>20</sup> is selected from H, halo, C<sub>1</sub>-C<sub>6</sub>alkyl, C<sub>1</sub>-C<sub>6</sub>haloalkyl, deuterated C<sub>1</sub>-C<sub>6</sub>alkyl, —CN, —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup>, —R<sup>8</sup>, —(CR<sup>9</sup>)<sub>n</sub>R<sup>8</sup>, —(CR<sup>9</sup>)<sub>n</sub>O(CR<sup>9</sup>)<sub>n</sub>R<sup>6</sup>, —(CR<sup>9</sup>)<sub>n</sub>C(=O)R<sup>4</sup>, —(CR<sup>9</sup>)<sub>n</sub>OR<sup>4</sup> and —OR<sup>4</sup>.
18. The compound of claim 1, wherein m is 1 and R<sup>20</sup> is selected from H, —F, —CH<sub>3</sub>, —CF<sub>3</sub>, —CD<sub>3</sub>, —CN, —OCHF<sub>2</sub>, —CH<sub>2</sub>CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>OH, —CH<sub>2</sub>OCH<sub>2</sub>CF<sub>3</sub>, —CH<sub>2</sub>CH<sub>2</sub>C(=O)CH<sub>3</sub>, —CH<sub>2</sub>OCH<sub>3</sub> and —OCH<sub>3</sub>.
19. The compound of claim 1, wherein m is 1 and R<sup>20</sup> is H or —CH<sub>3</sub>.
20. (canceled)
21. (canceled)
22. The compound of claim 1, wherein:  
R<sup>8</sup> is selected from phenyl, morpholinyl, cyclopropyl, pyridinyl, pyridine-3-yl, pyridine-4-yl, pyrazolyl, pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, pyrrolyl, triazolyl, 1H-1,2,3-triazol-4-yl, 4H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, thiazolyl, thiazol-4-yl, thiazol-5-yl, isoxazolyl and isoxazol-4-yl, each of which is unsubstituted or each of which is substituted with 1-3 substituents independently selected from F, —CH<sub>3</sub>, —C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>OH, —CH<sub>2</sub>OCH<sub>3</sub>, —C(O)NHCH<sub>3</sub>, —NH<sub>2</sub> and —OCH<sub>3</sub>.
23. (canceled)
24. The compound of claim 1 selected from:  
N-{5-[5-(2-cyanoethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;  
tert-butyl N-{2-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]ethyl}carbamate;  
N-{5-[5-(3-methoxypropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;  
N-(5-{5-[2-(diethylcarbamoyl)ethyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide);  
N-{2-methyl-5-[5-(3-oxobutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;  
tert-butyl N-{[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate;  
ethyl 2-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]acetate;
- N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;  
N-{5-[5-(3-hydroxybutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;  
N-{5-[5-(2-ethoxyethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;  
N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;  
N-{5-[5-(ethoxymethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;  
tert-butyl N-[(1S)-1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]ethyl]carbamate;  
N-(5-{5-[(1R)-1-methoxyethyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide);  
N-{2-methyl-5-[5-(3,3,3-trifluoro-2-hydroxy-2-methylpropyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;  
N-(2-methyl-5-{5-[3,3,3-trifluoro-2-hydroxy-2-(trifluoromethyl)propyl]-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide);  
N-{5-[5-(1,3-dihydroxy-2-methanesulfonamidopropan-2-yl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;  
N-(5-{5-[(1R)-1-methanesulfonamidoethyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide);  
tert-butyl N-{[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}-N-methylcarbamate;  
N-{5-[5-(ethanesulfonamidomethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;  
tert-butyl N-ethyl-N-{[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate;  
N-(5-{5-[(N-ethylmethanesulfonamido)methyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide);  
methyl N-ethyl-N-{[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate;  
N-(2-methyl-5-{5-[(2,2,2-trifluoroacetamido)methyl]-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide);  
N-{2-methyl-5-[5-(propane-2-sulfonamidomethyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide);  
N-(5-{5-[(2-methoxyethoxy)methyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide);  
tert-butyl 2-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]acetate;  
N-(2-methyl-5-{5-[2-(2,2,2-trifluoroethoxy)ethyl]-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide);  
ethyl N-{[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate;  
propan-2-yl N-{[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate;

- N-(2-methyl-5-[5-[(2R)-3,3,3-trifluoro-2-hydroxypropyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- N-(5-[5-[(2-ethoxyethoxy)methyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- N-[2-methyl-5-(5-[2-(propan-2-yloxy)ethoxy]methyl)-1,2,4-oxadiazol-3-yl]phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- N-[5-(5-[2-(tert-butoxy)ethoxy]methyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- N-(2-methyl-5-[5-[(3,3,3-trifluoropropanamido)methyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- 6-fluoro-N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;
- 6-fluoro-N-(5-[5-[(2-methoxyethoxy)methyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- ethyl N-{{3-(3-{6-fluoroimidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl}methyl}carbamate;
- N-(2-methyl-5-[5-[(2,2,2-trifluoroethoxy)methyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- 2,2-difluoroethyl N-{{3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl}methyl}carbamate;
- methyl N-{{3-[4-methyl-3-(7-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-4-yl]imidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate;
- N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(1-methyl-1H-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamide;
- N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-(1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide;
- 6-(1-methyl-1H-pyrazol-4-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- 6-[1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl]-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- N-(5-[[5-(1-hydroxy-2-methylpropan-2-yl)-1,2,4-oxadiazol-3-yl]amino]-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-(1,3-thiazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide;
- 6-(2,4-dimethyl-1,3-thiazol-5-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- 6-(3,5-dimethyl-1,2-oxazol-4-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-methylimidazo[1,2-a]pyridine-3-carboxamide;
- N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-4-yl}imidazo[1,2-a]pyridine-3-carboxamide;
- 5,6,7,8-tetradeutero-N-{2-methyl-5-[5-(3-methylbut-2-en-1-yl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;
- 5,6,7,8-tetradeutero-N-(5-[5-[(2-methoxyethoxy)methyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- 5,6,7,8-tetradeutero-N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;
- propan-2-yl 3-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]propanoate;
- N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-methoxyimidazo[1,2-a]pyridine-3-carboxamide;
- N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-methylimidazo[1,2-a]pyridine-3-carboxamide;
- N-(5-[5-[(2-methoxyethoxy)methyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl)-6-methylimidazo[1,2-a]pyridine-3-carboxamide;
- N-{2-methyl-5-[5-(pentan-2-yl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;
- N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(morpholin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide;
- N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(2-oxo-1,3-oxazolidin-3-yl)imidazo[1,2-a]pyridine-3-carboxamide;
- N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(2-oxopyrrolidin-1-yl)imidazo[1,2-a]pyridine-3-carboxamide;
- N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide;
- 7-cyclopropyl-N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;
- 7-fluoro-N-(5-[5-[(2-hydroxy-2-methylpropyl)(methyl)amino]-1,2,4-oxadiazol-3-yl]-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- N-{2-methyl-5-[5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;
- 7-methyl-N-{2-methyl-5-[5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;
- N-(5-{5-[(2-fluoroethyl)amino]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide;
- 7-methyl-N-(2-methyl-5-[5-[(2-methylpropyl)amino]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- 7-fluoro-N-{2-methyl-5-[5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;
- 6-fluoro-N-{2-methyl-5-[5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;
- 6-methyl-N-{2-methyl-5-[5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;
- 5,6,7,8-tetradeutero-N-{2-methyl-5-[5-(4,4,4-trifluoro-3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;



- N-{2-methyl-5-[5-(3,3,3-trifluoropropyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;
- 7-methyl-N-(2-methyl-5-[5-(3S)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- 7-methyl-N-(2-methyl-5-[5-(3R)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- 7-methyl-N-(2-methyl-5-[5-[(2,2,2-trifluoroethoxy)methyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- 7-methyl-N-(2-methyl-5-[5-[(2,2,2-trifluoroethoxy)methyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- 6-methyl-N-(2-methyl-5-[5-[(2,2,2-trifluoroethoxy)methyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- N-{2-methyl-5-[5-(4,4,4-trifluorobutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;
- N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-(2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-(2-methylpyridin-3-yl)imidazo[1,2-a]pyridine-3-carboxamide;
- N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-(3-methylpyridin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide;
- 6-methyl-N-(2-methyl-5-[5-(3S)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- 6-fluoro-N-(2-methyl-5-[5-(3S)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- 7-fluoro-N-(2-methyl-5-[5-(3S)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- 6-methyl-N-(2-methyl-5-[5-(3R)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- 6-fluoro-N-(2-methyl-5-[5-(3R)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- 7-fluoro-N-(2-methyl-5-[5-(3R)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- 7-methyl-N-{2-methyl-5-[5-(4,4,4-trifluoro-3-methoxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;
- 6-(2,4-dimethyl-1,3-thiazol-5-yl)-N-(2-methyl-5-[5-(2,2,2-trifluoroethoxy)methyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- 6-(2-fluoropyridin-3-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- N-methyl-5-(3-[[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl]imidazo[1,2-a]pyridin-6-yl)pyridine-2-carboxamide;
- N-(5-[5-[(2,2-difluoroethoxy)methyl]-1,2,4-oxadiazol-3-yl]-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- N-{5-(5-[[1,3-difluoropropan-2-yl]oxy]methyl)-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- N-[2-methyl-5-(5-[[1,1,1-trifluoropropan-2-yl]oxy]methyl)-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- 6-(4-methyl-1,3-thiazol-5-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- 7-methyl-N-{2-methyl-5-[5-(4,4,4-trifluoro-3-hydroxybutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;
- 7-methyl-N-(2-methyl-5-[5-[(2R)-3,3,3-trifluoro-2-hydroxypropyl]-1,2,4-oxadiazol-3-yl]phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide;
- 6-(1-methyl-1H-pyrrol-2-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- 6-(4-methoxypyridin-3-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- 6-(2-aminopyridin-4-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- tert-butyl 2-[3,5-dimethyl-4-(3-[[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl]imidazo[1,2-a]pyridin-6-yl)-1H-pyrazol-1-yl]acetate;
- 6-[5-(1-hydroxyethyl)-4-methyl-1,3-thiazol-2-yl]-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- 6-(4,5-dimethyl-1,3-thiazol-2-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- 6-(1-[[2-(hydroxyethyl)carbamoyl]methyl]-3,5-dimethyl-1H-pyrazol-4-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- 6-[3,5-dimethyl-1-((2-(morpholin-4-yl)ethyl)carbamoyl)methyl]-1H-pyrazol-4-yl]-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- 6-carbamothioyl-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- N-(2-hydroxyethyl)-4-methyl-2-(3-[[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl]imidazo[1,2-a]pyridin-6-yl)-1,3-thiazole-5-carboxamide;
- 4-methyl-2-(3-[[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl]imidazo[1,2-a]pyridin-6-yl)-N-[2-(4-methylpiperazin-1-yl)ethyl]-1,3-thiazole-5-carboxamide;
- 4-methyl-2-(3-[[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl]imidazo[1,2-a]pyridin-6-yl)-N-[3-(4-methylpiperazin-1-yl)propyl]-1,3-thiazole-5-carboxamide;
- 4-methyl-2-(3-[[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl]imidazo[1,2-a]pyridin-6-yl)-N-[2-(morpholin-4-yl)ethyl]-1,3-thiazole-5-carboxamide;

- 8-amino-N-{5-[5-(3-hydroxy-3-methylbutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;
- 4-methyl-5-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-1,3-thiazole-2-carboxylic acid;
- 4-methyl-5-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-N-[2-(4-methylpiperazin-1-yl)ethyl]-1,3-thiazole-2-carboxamide;
- 2-methyl-4-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]butan-2-yl 2-aminoacetate;
- (2R)-1,1,1-trifluoro-2-methyl-4-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]butan-2-yl(2R)-2-amino-3-methylbutanoate;
- (2S)-1,1,1-trifluoro-2-methyl-4-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]butan-2-yl (2R)-2-amino-3-methylbutanoate;
- 7-methyl-N-{2-methyl-5-[5-(4,4,4-trifluoro-3-hydroxybutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;
- 7-methyl-N-(2-methyl-5-{5-[3,3,3-trifluoro-2-hydroxy-2-(trifluoromethyl)propyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- 6-[1-(2-hydroxyethyl)-3,5-dimethyl-1H-pyrazol-4-yl]-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- 6-(5-acetyl-4-methyl-1,3-thiazol-2-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- 6-(3-methyl-1H-pyrazol-4-yl)-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- N,4-dimethyl-2-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-1,3-thiazole-5-carboxamide;
- 4-methyl-2-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-1,3-thiazole-5-carboxamide;
- 6-{3,5-dimethyl-1-[(methylcarbonyl)methyl]-1H-pyrazol-4-yl}-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- ethyl 4-methyl-5-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-1,3-thiazole-2-carboxylate;
- 4-methyl-5-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-N-[2-(morpholin-4-yl)ethyl]-1,3-thiazole-2-carboxamide;
- N-(2-hydroxyethyl)-4-methyl-5-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-1,3-thiazole-2-carboxamide;
- 4-methyl-5-(3-{[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]carbamoyl}imidazo[1,2-a]pyridin-6-yl)-1,3-thiazole-2-carboxamide;
- 6-[2-(hydroxymethyl)-4-methyl-1,3-thiazol-5-yl]-N-[2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- N-(2-methyl-5-{5-[1-(2,2,2-trifluoroethoxy)ethyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- dimethyl (2R)-1,1,1-trifluoro-2-methyl-4-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]butan-2-yl phosphate;
- {[(2R)-1,1,1-trifluoro-2-methyl-4-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]butan-2-yl]oxy}phosphonic acid;
- dimethyl (2S)-1,1,1-trifluoro-2-methyl-4-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]butan-2-yl phosphate;
- {[(2S)-1,1,1-trifluoro-2-methyl-4-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]butan-2-yl]oxy}phosphonic acid, and
- 1,1,1-trifluoro-2-methyl-4-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]butan-2-yl (2S)-2-aminopropanoate.
- 25.** The compound of claim **1** selected from:  
 N-(5-{[5-(1-hydroxy-2-methylpropan-2-yl)-1,2,4-oxadiazol-3-yl]amino}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;
- 7-methyl-N-(2-methyl-5-{5-[(3S)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide, and
- 7-methyl-N-(2-methyl-5-{5-[(3R)-4,4,4-trifluoro-3-hydroxy-3-methylbutyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide.
- 26.** A pharmaceutical composition comprising a therapeutically effective amount a compound of claim **1** and a pharmaceutically acceptable carrier.
- 27.** (canceled)
- 28.** (canceled)
- 29.** (canceled)
- 30.** (canceled)
- 31.** (canceled)
- 32.** (canceled)
- 33.** (canceled)
- 34.** (canceled)
- 35.** (canceled)

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