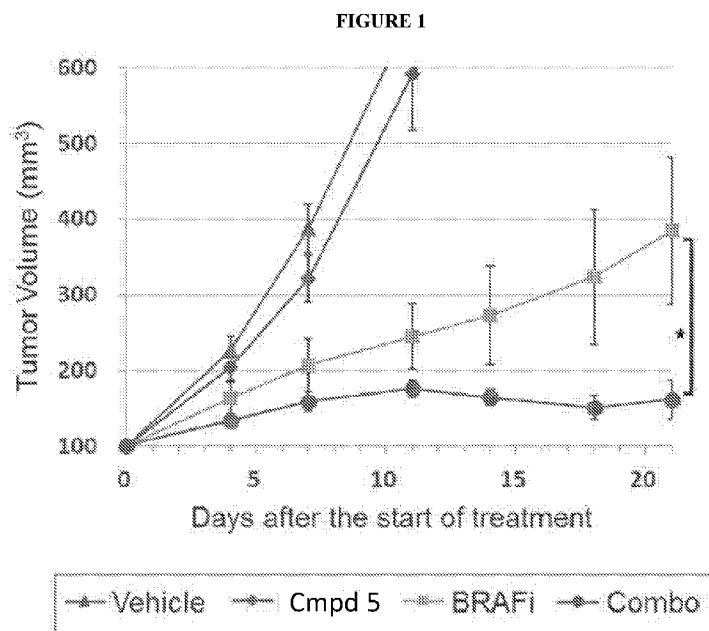




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(54) Title: IMIDODICARBONIMIDIC DIAMIDE ANALOGS



(57) Abstract: The present disclosure is directed to imidodicarbonimidic diamide compounds, and their pharmaceutically acceptable salts, solvates, or stereoisomers thereof. This disclosure also provides compositions and the use of such compositions in method of treating cancer, diabetes, or polycystic ovarian syndrome.



TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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## IMIDODICARBONIMIDIC DIAMIDE ANALOGS

### CROSS-REFERENCE

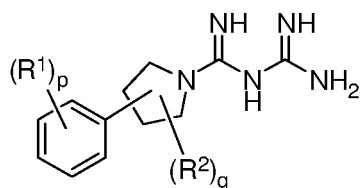
[0001] This application claims benefit of U.S. Provisional Application No. 62/345,708, filed on June 3, 2016, which is herein incorporated by reference in its entirety.

### BACKGROUND OF INVENTION

[0002] Despite its efficacy as a hypoglycemic agent, phenformin is no longer available for the treatment of diabetes in the United States due to its association with an increased risk of lactic acidosis. Metformin, another biguanide, has replaced phenformin in the United States for the treatment of diabetes since the incidence of lactic acidosis associated with metformin is significantly less than that observed with phenformin. Metformin has also demonstrated improved survival in several cancers including breast, colon, pancreatic, and prostate. However, despite this anti-cancer activity, metformin is unlikely to offer true benefit to a wide range of cancer patients due to a lack of potency. Thus, there remains a need for improved biguanide therapeutics.

### SUMMARY OF THE INVENTION

[0003] In one aspect, provided herein is a compound of Formula (I) having the structure:



Formula (I);

wherein:

each R<sup>1</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -OC(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -N(R<sup>4</sup>)C(O)R<sup>3</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -N(R<sup>4</sup>)C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, -N(R<sup>4</sup>)S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>;

each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R<sup>3</sup> is independently C<sub>1-6</sub>alkyl;

each R<sup>4</sup> is independently H or C<sub>1-6</sub>alkyl;

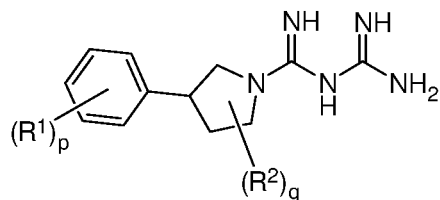
each R<sup>5</sup> and each R<sup>6</sup> are independently H or C<sub>1-6</sub>alkyl; or R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form an optionally substituted C<sub>1-6</sub>heterocycloalkyl;

p is 0, 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

**[0004]** In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, having the structure of Formula (Ia):

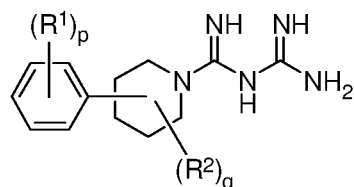


Formula (Ia). In some embodiments is a compound of

Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen,  $-OR^4$ ,  $-NR^4R^4$ ,  $C_{1-6}$ alkyl,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy, optionally substituted  $C_{1-6}$ heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl,  $-C(O)R^3$ ,  $-CO_2R^4$ ,  $-C(O)NR^5R^6$ ,  $-S(O)_2R^3$ , or  $-S(O)_2NR^5R^6$ . In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen,  $-OR^4$ ,  $-NR^4R^4$ ,  $C_{1-6}$ alkyl,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy,  $-CO_2R^4$ , or  $-C(O)NR^5R^6$ . In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen,  $-OR^4$ ,  $C_{1-6}$ alkyl,  $C_{1-6}$ haloalkyl, or  $C_{1-6}$ haloalkoxy. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen,  $-OR^4$ , or  $C_{1-6}$ alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-OCH_3$ . In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $C_{1-6}$ alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 2. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 1. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 0. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkyl or  $C_{1-6}$ alkoxy. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkyl. In some embodiments is a compound of Formula (I), or a

pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 2. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 1. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 0.

**[0005]** In another aspect, provided herein is a compound of Formula (II) having the structure:



Formula (II);

wherein:

each  $R^1$  is independently halogen,  $-CN$ ,  $-NO_2$ ,  $-OR^4$ ,  $-NR^4R^4$ ,  $C_{1-6}$ alkyl,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy, optionally substituted  $C_{1-6}$ heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl,  $-C(O)R^3$ ,  $-OC(O)R^3$ ,  $-CO_2R^4$ ,  $-N(R^4)C(O)R^3$ ,  $-C(O)NR^5R^6$ ,  $-N(R^4)C(O)NR^5R^6$ ,  $-S(O)_2R^3$ ,  $-N(R^4)S(O)_2R^3$ , or  $-S(O)_2NR^5R^6$ ;

each  $R^2$  is independently  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy, optionally substituted  $C_{1-6}$ heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each  $R^3$  is independently  $C_{1-6}$ alkyl;

each  $R^4$  is independently H or  $C_{1-6}$ alkyl;

each  $R^5$  and each  $R^6$  are independently H or  $C_{1-6}$ alkyl; or  $R^5$  and  $R^6$  together with the nitrogen atom to which they are attached form an optionally substituted  $C_{1-6}$ heterocycloalkyl;

p is 1, 2, 3, 4, or 5; and

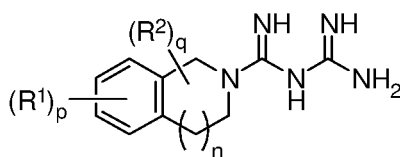
q is 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

**[0006]** In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen,  $-OR^4$ ,  $-NR^4R^4$ ,  $C_{1-6}$ alkyl,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy, optionally substituted  $C_{1-6}$ heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl,  $-C(O)R^3$ ,  $-CO_2R^4$ ,  $-C(O)NR^5R^6$ ,  $-S(O)_2R^3$ , or  $-S(O)_2NR^5R^6$ . In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen,  $-OR^4$ ,  $-NR^4R^4$ ,  $C_{1-6}$ alkyl,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy,  $-CO_2R^4$ , or  $-C(O)NR^5R^6$ . In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen,  $-OR^4$ ,  $C_{1-6}$ alkyl,  $C_{1-6}$ haloalkyl,

or C<sub>1-6</sub>haloalkoxy. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -OR<sup>4</sup>, or C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is -OCH<sub>3</sub>. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 1. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 2. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 3. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 2. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 1. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 0.

**[0007]** In another aspect, provided herein is a compound having the structure of Formula (III):



Formula (III);

wherein:

each R<sup>1</sup> is independently halogen, -CN, -NO<sub>2</sub>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-</sub>

<sub>6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl,

optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -OC(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -N(R<sup>4</sup>)C(O)R<sup>3</sup>, -

C(O)NR<sup>5</sup>R<sup>6</sup>, -N(R<sup>4</sup>)C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, -N(R<sup>4</sup>)S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>;

each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R<sup>3</sup> is independently C<sub>1-6</sub>alkyl;

each R<sup>4</sup> is independently H or C<sub>1-6</sub>alkyl;

each R<sup>5</sup> and each R<sup>6</sup> are independently H or C<sub>1-6</sub>alkyl; or R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form an optionally substituted C<sub>1-6</sub>heterocycloalkyl;

n is 0 or 1;

p is 1, 2, 3, or 4; and

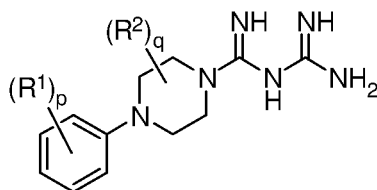
q is 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

**[0008]** In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, -CO<sub>2</sub>R<sup>4</sup>, or -C(O)NR<sup>5</sup>R<sup>6</sup>. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, or C<sub>1-6</sub>haloalkoxy. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen or C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 1. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 2. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 3. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 2. In some

embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 1. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 0. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each n is 0. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each n is 1.

**[0009]** In another aspect, provided herein is a compound having the structure of Formula (IV):



Formula (IV);

wherein:

each  $R^1$  is independently  $-CN$ ,  $-NR^4R^4$ ,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy, optionally substituted  $C_{1-6}$ heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl,  $-C(O)R^3$ ,  $-OC(O)R^3$ ,  $-CO_2R^4$ ,  $-N(R^4)C(O)R^3$ ,  $-C(O)NR^5R^6$ ,  $-N(R^4)C(O)NR^5R^6$ ,  $-S(O)_2R^3$ ,  $-N(R^4)S(O)_2R^3$ , or  $-S(O)_2NR^5R^6$ ;

each  $R^2$  is independently  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy, optionally substituted  $C_{1-6}$ heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each  $R^3$  is independently  $C_{1-6}$ alkyl;

each  $R^4$  is independently H or  $C_{1-6}$ alkyl;

each  $R^5$  and each  $R^6$  are independently H or  $C_{1-6}$ alkyl; or  $R^5$  and  $R^6$  together with the nitrogen atom to which they are attached form an optionally substituted  $C_{1-6}$ heterocycloalkyl;

p is 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

**[0010]** In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $-NR^4R^4$ ,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy, optionally substituted  $C_{1-6}$ heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl,  $-C(O)R^3$ ,  $-CO_2R^4$ ,  $-C(O)NR^5R^6$ ,  $-S(O)_2R^3$ , or  $-S(O)_2NR^5R^6$ . In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $-NR^4R^4$ ,  $C_{1-6}$ haloalkyl,  $C_{1-6}$



$_6$ haloalkoxy,  $-\text{CO}_2\text{R}^4$ , or  $-\text{C}(\text{O})\text{NR}^5\text{R}^6$ . In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^1$  is independently  $\text{C}_{1-6}$ haloalkyl or  $\text{C}_{1-6}$ haloalkoxy. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 1. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 2. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 3. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^2$  is independently  $\text{C}_{1-6}$ alkyl or  $\text{C}_{1-6}$ alkoxy. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^2$  is independently  $\text{C}_{1-6}$ alkyl. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $q$  is 2. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $q$  is 1. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $q$  is 0.

**[0011]** In another aspect, provided herein is a pharmaceutical composition comprising a compound of Formula (I), (Ia), (II), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient.

**[0012]** In another aspect, provided herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (I), (Ia), (II), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (I), (Ia), (II), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein the cancer is selected from IDH1 mutant cancers and cancers with LKB1 deficient tumors.

**[0013]** In another aspect, provided herein is a method of treating diabetes in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (I), (Ia), (II), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (I), (Ia), (II), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein the diabetes is type 2 diabetes.

**[0014]** In another aspect, provided herein is a method of treating polycystic ovarian syndrome in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (I), (Ia), (II), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

**[0015]** In some embodiments, the methods described herein further comprise the administration of a second therapeutic agent. In some embodiments, the second therapeutic agent is a BRAF inhibitor. In some embodiments, the second therapeutic agent is a BRAF inhibitor selected from dabrafenib, vemurafenib, encorafenib, TAK-580, LY3009120, BGB-283, HM955573, and PLX8394. In some embodiments, the second therapeutic agent is an mTOR inhibitor. In some embodiments, the second therapeutic agent is an mTOR inhibitor selected from everolimus, TAK-228, AZD2014, LY3023414, and gedatolisib.

**[0016]** In another aspect, provided herein is a method of increasing the bioavailability of a compound of Formula (I), (Ia), (II), (III), or (IV) in a subject comprising administering to a subject a compound of Formula (I), (Ia), (II), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

**[0017]** In another aspect, provided herein is a method of decreasing the metabolism of a compound of Formula (I), (Ia), (II), (III), or (IV) in a subject comprising administering to a subject a compound of Formula (I), (Ia), (II), (III), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

### **INCORPORATION BY REFERENCE**

**[0018]** All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

### **BRIEF DESCRIPTION OF THE DRAWINGS**

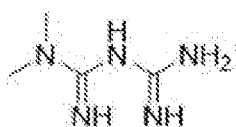
**[0019]** Figure 1 shows tumor volume of a mutant BRAF melanoma (Colo829) through 21 days of treatment with Compound 5, a BRAF inhibitor, or a Compound 5/BRAF inhibitor combination.

**[0020]** Figure 2 shows tumor volume of a mutant KRAS, LKB1(-) NSCLC (A549) through 21 days of treatment with Compound 5, an mTOR inhibitor, or a Compound 5/mTOR inhibitor combination.

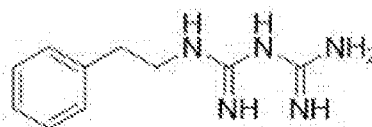
## DETAILED DESCRIPTION

**[0021]** Metformin is an approved type 2 diabetes drug that has demonstrated anti-cancer activity in a number of retrospective analyses. Beginning in 2005, a number of studies have demonstrated improved survival in a range of different cancers, including breast, colon, pancreatic, and prostate. However, other studies found no improvement in survival. Although metformin has shown some anti-cancer activity, the data suggests that the compound lacks the potency to benefit a wide range of cancer patients. Thus, a compound with improved potency/efficacy over metformin would offer substantial benefit to many cancer patients.

**[0022]** In non-clinical studies, phenformin, a member of the biguanide structural class that includes metformin, consistently demonstrates improved potency and activity against a wider set of cancer types than metformin. Phenformin was approved to treat type 2 diabetes in 1959, however the FDA rescinded its approval in the United States in 1978 due to its association with an increased risk of lactic acidosis (0.6 events per 1,000 patient years) compared to metformin (0.1 events per 1,000 patient years). Thus there remains a need to identify compounds that retain phenformin's superior anticancer and anti-diabetes activity while reducing the risk of lactic acidosis.



Metformin



Phenformin

**[0023]** Since approval was rescinded in 1978 researchers have demonstrated that phenformin is metabolized by the cytochrome P450 2D6 to an inactive metabolite. A large fraction of the human population has a functional deficiency in the CYP2D6 enzyme that leads to a significant increase in the levels of phenformin in this poor metabolizer population. 2D6 polymorphisms in humans leads to large phenformin metabolism variability ranging from essentially no metabolism in poor metabolizers to 200-fold higher metabolism in ultrarapid metabolizers. It is now recognized that in 2D6 poor metabolizers there is a significant increase in active phenformin levels leading to increased lactate levels that contributes to the development of lactic acidosis and places this patient group at increased risk. In addition there are a significant number of concomitant drugs prescribed to cancer patients that either inhibit or are substrates of 2D6 that could lead to reduced phenformin metabolism further increasing the risk of lactic acidosis in this patient population.

**[0024]** Conversely, the high CYP2D6 metabolizers have low levels of phenformin upon dosing, thereby decreasing the desired efficacy.

[0025] Given this, it is desirable to provide a compound that has the beneficial activities of phenformin and may also have other benefits including decreased metabolic liability to extend its pharmacological effective life, reduce adverse side effects, to decrease population pharmacokinetic variability, decrease its potential for dangerous drug-drug interactions, or to decrease the risk of phenformin induced lactic acidosis.

[0026] Disclosed herein are constrained analogues of phenformin which have reduced 2D6 metabolism, while maintaining many of the other properties of phenformin including potency, thereby providing an opportunity to develop improved type 2 diabetes and cancer drugs without phenformin's risk of increased 2D6 mediated lactic acidosis.

[0027] At a cellular level, metformin stimulates AMP-activated protein kinase (AMPK) activation. Metformin-induced activation of AMPK inhibits downstream mTORC1 which integrates signals from a diverse array of signaling pathways to regulate pancreatic cancer cell survival, growth and metastasis. It is postulated that metformin inhibits pancreatic cancer growth in part via AMPK-mediated inhibition of mTORC1 activation. Independent data show that metformin also disrupts critical cross-talk between insulin/IGF-1 and GPCR signaling pathways and possibly ERK and Rag GTPase signaling. Further laboratory studies show that metformin markedly inhibits growth of human pancreatic cancer cells xenografted in nude mice. This preclinical work is supported by clinical cohort studies showing that metformin users have a reduced risk of pancreatic cancer; and that metformin use correlates with a survival benefit in patients with diabetes and pancreatic cancer. In the latter study, the median survival is prolonged by four months in cancer patients who are metformin users compared to non-users. It is notable that anticancer effects of metformin increase with increasing doses and/or with IV as compared to oral administration.

### **Certain Terminology**

[0028] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below.

[0029] As used herein, the singular forms "a," "an," and "the" may refer to plural articles unless specifically stated otherwise. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

**[0030]** Unless specific definitions are provided, the nomenclature employed in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those recognized in the field. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. Standard techniques can be used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Reactions and purification techniques can be performed e.g., using kits of manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures can be generally performed of conventional methods and as described in various general and more specific references that are cited and discussed throughout the present specification.

**[0031]** It is to be understood that the methods and compositions described herein are not limited to the particular methodology, protocols, cell lines, constructs, and reagents described herein and as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the methods, compounds, compositions described herein.

**[0032]** As used herein, C<sub>1</sub>-C<sub>x</sub> includes C<sub>1</sub>-C<sub>2</sub>, C<sub>1</sub>-C<sub>3</sub> . . . C<sub>1</sub>-C<sub>x</sub>. C<sub>1</sub>-C<sub>x</sub> refers to the number of carbon atoms that make up the moiety to which it designates (excluding optional substituents).

**[0033]** An "alkyl" group refers to an aliphatic hydrocarbon group. The alkyl group may or may not include units of unsaturation. The alkyl moiety may be a "saturated alkyl" group, which means that it does not contain any units of unsaturation (i.e. a carbon-carbon double bond or a carbon-carbon triple bond). The alkyl group may also be an "unsaturated alkyl" moiety, which means that it contains at least one unit of unsaturation. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

**[0034]** The "alkyl" group may have 1 to 6 carbon atoms (whenever it appears herein, a numerical range such as "1 to 6" refers to each integer in the given range; e.g., "1 to 6 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 6 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group of the compounds described herein may be designated as "C<sub>1</sub>-C<sub>6</sub> alkyl" or similar designations. By way of example only, "C<sub>1</sub>-C<sub>6</sub> alkyl" indicates that there are one to six carbon atoms in the alkyl chain, *i.e.*, the alkyl chain is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, iso-pentyl, neo-pentyl, hexyl, propen-3-yl (allyl), cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl. Alkyl

groups can be substituted or unsubstituted. Depending on the structure, an alkyl group can be a monoradical or a diradical (i.e., an alkylene group).

**[0035]** An “alkoxy” refers to a “-O-alkyl” group, where alkyl is as defined herein.

**[0036]** The term “alkenyl” refers to a type of alkyl group which contains at least one double bond that is not part of an aromatic group. Non-limiting examples of an alkenyl group include  $-\text{CH}=\text{CH}_2$ ,  $-\text{C}(\text{CH}_3)=\text{CH}_2$ ,  $-\text{CH}=\text{CHCH}_3$ ,  $-\text{CH}=\text{C}(\text{CH}_3)_2$  and  $-\text{C}(\text{CH}_3)=\text{CHCH}_3$ . The alkenyl moiety may be branched or straight chain. Alkenyl groups can be substituted or unsubstituted. Depending on the structure, an alkenyl group can be a monoradical or a diradical (i.e., an alkenylene group).

**[0037]** The term “alkynyl” refers to a type of alkyl group which contains at least one triple bond. Non-limiting examples of an alkynyl group include  $-\text{C}\equiv\text{CH}$ ,  $-\text{C}\equiv\text{CCH}_3$ ,  $-\text{C}\equiv\text{CCH}_2\text{CH}_3$  and  $-\text{C}\equiv\text{CCH}_2\text{CH}_2\text{CH}_3$ . Alkynyl groups can be substituted or unsubstituted. Depending on the structure, an alkynyl group can be a monoradical or a diradical (i.e., an alkynylene group).

**[0038]** “Amino” refers to a  $-\text{NH}_2$  group.

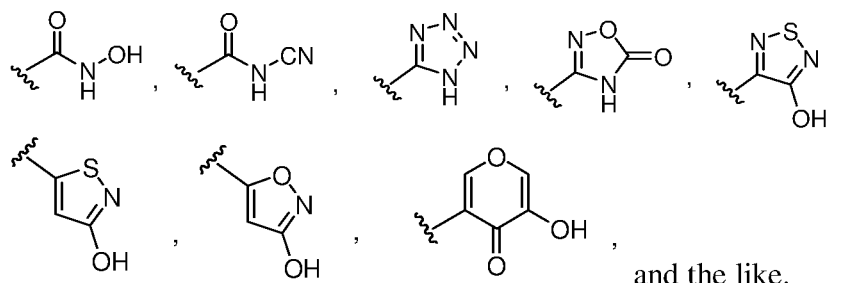
**[0039]** The term “alkylamine” or “alkylamino” refers to the  $-\text{N}(\text{alkyl})_x\text{H}_y$  group, where alkyl is as defined herein and x and y are selected from the group x=1, y=1 and x=2, y=0. When x=2, the alkyl groups, taken together with the nitrogen to which they are attached, can optionally form a cyclic ring system. “Dialkylamino” refers to a  $-\text{N}(\text{alkyl})_2$  group, where alkyl is as defined herein.

**[0040]** The term “aromatic” refers to a planar ring having a delocalized  $\pi$ -electron system containing  $4n+2$   $\pi$  electrons, where n is an integer. Aromatic rings can be formed from five, six, seven, eight, nine, or more than nine atoms. Aromatics can be optionally substituted. The term “aromatic” includes both aryl groups (e.g., phenyl, naphthalenyl) and heteroaryl groups (e.g., pyridinyl, quinolinyl).

**[0041]** As used herein, the term “aryl” refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl rings can be formed by five, six, seven, eight, nine, or more than nine carbon atoms. Aryl groups can be optionally substituted. Examples of aryl groups include, but are not limited to phenyl, and naphthalenyl. Depending on the structure, an aryl group can be a monoradical or a diradical (i.e., an arylene group).

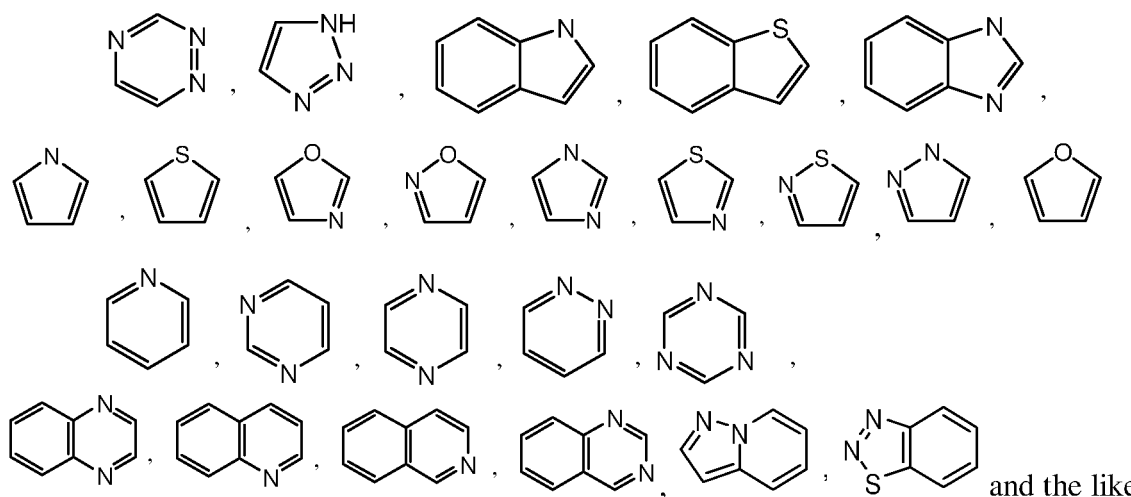
**[0042]** “Carboxy” refers to  $-\text{CO}_2\text{H}$ . In some embodiments, carboxy moieties may be replaced with a “carboxylic acid bioisostere”, which refers to a functional group or moiety that exhibits similar physical and/or chemical properties as a carboxylic acid moiety. A carboxylic acid bioisostere has similar biological properties to that of a carboxylic acid group. A compound with a carboxylic acid moiety can have the carboxylic acid moiety exchanged with a carboxylic acid

bioisostere and have similar physical and/or biological properties when compared to the carboxylic acid-containing compound. For example, in one embodiment, a carboxylic acid bioisostere would ionize at physiological pH to roughly the same extent as a carboxylic acid group. Examples of bioisosteres of a carboxylic acid include, but are not limited to,



**[0043]** The term “cycloalkyl” refers to a monocyclic or polycyclic non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. Cycloalkyls may be saturated, or partially unsaturated. Cycloalkyls may be fused with an aromatic ring (in which case the cycloalkyl is bonded through a non-aromatic ring carbon atom). Unless otherwise noted, cycloalkyl groups include groups having from 3 to 10 ring atoms.

**[0044]** The terms “heteroaryl” or, alternatively, “heteroaromatic” refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. An *N*-containing “heteroaromatic” or “heteroaryl” moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. Polycyclic heteroaryl groups may be fused or non-fused. Illustrative examples of heteroaryl groups include the following moieties:



**[0045]** A “heterocycloalkyl” group or “heteroalicyclic” group refers to a cycloalkyl group, wherein at least one skeletal ring atom is a heteroatom selected from nitrogen, oxygen and sulfur. The radicals may be fused with an aryl or heteroaryl. Unless otherwise noted, heterocycloalkyls have from 2 to 10 carbons in the ring.

**[0046]** The term “halo” or, alternatively, “halogen” means fluoro, chloro, bromo, and iodo.

**[0047]** The term “haloalkyl” refers to an alkyl group that is substituted with one or more halogens. The halogens may be the same or they may be different. Non-limiting examples of haloalkyls include  $-\text{CH}_2\text{Cl}$ ,  $-\text{CF}_3$ ,  $-\text{CHF}_2$ ,  $-\text{CH}_2\text{CF}_3$ ,  $-\text{CF}_2\text{CF}_3$ ,  $-\text{CF}(\text{CH}_3)_3$ , and the like.

**[0048]** The term “haloalkoxy” refers to an alkoxy group that is substituted with one or more halogens. The halogens may be the same or they may be different.

**[0049]** The terms “fluoroalkyl” and “fluoroalkoxy” include alkyl and alkoxy groups, respectively, that are substituted with one or more fluorine atoms. Non-limiting examples of fluoroalkyls include  $-\text{CF}_3$ ,  $-\text{CHF}_2$ ,  $-\text{CH}_2\text{F}$ ,  $-\text{CH}_2\text{CF}_3$ ,  $-\text{CF}_2\text{CF}_3$ ,  $-\text{CF}_2\text{CF}_2\text{CF}_3$ ,  $-\text{CF}(\text{CH}_3)_3$ , and the like. Non-limiting examples of fluoroalkoxy groups, include  $-\text{OCF}_3$ ,  $-\text{OCHF}_2$ ,  $-\text{OCH}_2\text{F}$ ,  $-\text{OCH}_2\text{CF}_3$ ,  $-\text{OCF}_2\text{CF}_3$ ,  $-\text{OCF}_2\text{CF}_2\text{CF}_3$ ,  $-\text{OCF}(\text{CH}_3)_2$ , and the like.

**[0050]** The term “heteroalkyl” refers to an alkyl radical where one or more skeletal chain atoms is selected from an atom other than carbon, *e.g.*, oxygen, nitrogen, sulfur, phosphorus, silicon, or combinations thereof. The heteroatom(s) may be placed at any interior position of the heteroalkyl group. Examples include, but are not limited to,  $-\text{CH}_2\text{-O-CH}_3$ ,  $-\text{CH}_2\text{-CH}_2\text{-O-CH}_3$ ,  $-\text{CH}_2\text{-NH-CH}_3$ ,  $-\text{CH}_2\text{-CH}_2\text{-NH-CH}_3$ ,  $-\text{CH}_2\text{-N}(\text{CH}_3)\text{-CH}_3$ ,  $-\text{CH}_2\text{-CH}_2\text{-NH-CH}_3$ ,  $-\text{CH}_2\text{-CH}_2\text{-N}(\text{CH}_3)\text{-CH}_3$ ,  $-\text{CH}_2\text{-S-CH}_2\text{-CH}_3$ ,  $-\text{CH}_2\text{-CH}_2\text{-S}(\text{O})\text{-CH}_3$ ,  $-\text{CH}_2\text{-CH}_2\text{-S}(\text{O})_2\text{-CH}_3$ ,  $-\text{CH}_2\text{-NH-OCH}_3$ ,  $-\text{CH}_2\text{-O-Si}(\text{CH}_3)_3$ ,  $-\text{CH}_2\text{-CH=N-OCH}_3$ , and  $-\text{CH=CH-N}(\text{CH}_3)\text{-CH}_3$ . In addition, up to two heteroatoms may be consecutive, such as, by way of example,  $-\text{CH}_2\text{-NH-OCH}_3$  and  $-\text{CH}_2\text{-O-Si}(\text{CH}_3)_3$ . Excluding the number of heteroatoms, a “heteroalkyl” may have from 1 to 6 carbon atoms.

**[0051]** The term “bond” or “single bond” refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure.

**[0052]** The term “moiety” refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

**[0053]** The term “optionally substituted” or “substituted” means that the referenced group may be substituted with one or more additional group(s) individually and independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl,  $-\text{OH}$ , alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone,  $-\text{CN}$ , alkyne,  $\text{C}_1\text{-C}_6$ alkylalkyne, halo, acyl, acyloxy,  $-\text{CO}_2\text{H}$ ,  $-\text{CO}_2\text{-alkyl}$ , nitro, haloalkyl, fluoroalkyl, and amino, including mono- and di-substituted amino groups (*e.g.*  $-\text{NH}_2$ ,  $-\text{NHR}$ ,  $-\text{N}(\text{R})_2$ ), and the protected derivatives thereof. By way of example, an optional substituent may be  $\text{L}^s\text{R}^s$ , wherein each  $\text{L}^s$  is independently selected from a bond,  $-\text{O}-$ ,  $-\text{C}(=\text{O})-$ ,  $-\text{S}-$ ,  $-\text{S}(=\text{O})-$ ,  $-\text{S}(=\text{O})_2-$ ,  $-\text{NH}-$ ,  $-\text{NHC}(\text{O})-$ ,  $-\text{C}(\text{O})\text{NH}-$ ,  $\text{S}(=\text{O})_2\text{NH}-$ ,  $-\text{NHS}(=\text{O})_2-$ ,  $-\text{OC}(\text{O})\text{NH}-$ ,  $-\text{NHC}(\text{O})\text{O}-$ ,  $-(\text{C}_1\text{-C}_6\text{alkyl})-$ , or  $-(\text{C}_2-$



C<sub>6</sub>alkenyl)-; and each R<sup>s</sup> is independently selected from among H, (C<sub>1</sub>-C<sub>6</sub>alkyl), (C<sub>3</sub>-C<sub>8</sub>cycloalkyl), aryl, heteroaryl, heterocycloalkyl, and C<sub>1</sub>-C<sub>6</sub>heteroalkyl.

**[0054]** The term “subject” refers to an animal, including, but not limited to, a primate (e.g., human), cow, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms “subject” and “patient” are used interchangeably herein in reference, for example, to a mammalian subject, such as a human subject.

**[0055]** The terms “treat,” “treating,” and “treatment” are meant to include alleviating or abrogating a disorder, disease, or condition; or one or more of the symptoms associated with the disorder, disease, or condition; or alleviating or eradicating the cause(s) of the disorder, disease, or condition itself.

**[0056]** The terms “prevent,” “preventing,” and “prevention” refer to a method of delaying or precluding the onset of a disorder, disease, or condition; and/or its attendant symptoms, barring a subject from acquiring a disease or reducing a subject’s risk of acquiring a disorder, disease, or condition.

**[0057]** The term “therapeutically effective amount” refers to the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disorder, disease, or condition being treated. The term “therapeutically effective amount” also refers to the amount of a compound that is sufficient to elicit the biological or medical response of a cell, tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor, or clinician.

**[0058]** The term “pharmaceutically acceptable carrier,” “pharmaceutically acceptable excipient,” “physiologically acceptable carrier,” or “physiologically acceptable excipient” refers to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent, or encapsulating material. Each component must be “pharmaceutically acceptable” in the sense of being compatible with the other ingredients of a pharmaceutical formulation. It must also be suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. *See, Remington: The Science and Practice of Pharmacy, 21st Edition; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; Handbook of Pharmaceutical Excipients, 5th Edition; Rowe et al., Eds., The Pharmaceutical Press and the American Pharmaceutical Association: 2005; and Handbook of Pharmaceutical Additives, 3rd Edition; Ash and Ash Eds., Gower Publishing Company: 2007; Pharmaceutical Preformulation and Formulation, Gibson Ed., CRC Press LLC: Boca Raton, FL, 2004).*

**[0059]** The term “pharmaceutical composition” refers to a mixture of a compound disclosed herein with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to, oral, injection, aerosol, parenteral, and topical administration. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

**[0060]** The term “carrier” defines a chemical compound that facilitates the incorporation of a compound into cells or tissues. For example dimethyl sulfoxide (DMSO) is a commonly utilized carrier as it facilitates the uptake of many organic compounds into the cells or tissues of an organism.

**[0061]** The terms “substantially pure” and “substantially homogeneous” mean sufficiently homogeneous to appear free of readily detectable impurities as determined by standard analytical methods used by one of ordinary skill in the art, including, but not limited to, thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC), nuclear magnetic resonance (NMR), and mass spectrometry (MS); or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, or biological and pharmacological properties, such as enzymatic and biological activities, of the substance. In certain embodiments, “substantially pure” or “substantially homogeneous” refers to a collection of molecules, wherein at least 50%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98%, at least 99%, or at least 99.5% of the molecules are a single compound, including a racemic mixture or single stereoisomer thereof, as determined by standard analytical methods.

**[0062]** The term “about” or “approximately” means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, “about” can mean with 1 or more standard deviations.

**[0063]** The terms “active ingredient” and “active substance” refer to a compound, which is administered, alone or in combination with one or more pharmaceutically acceptable excipients, to a subject for treating, preventing, or ameliorating one or more symptoms of a disorder or disease.

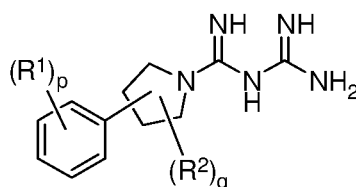
[0064] The terms “drug,” “therapeutic agent,” and “chemotherapeutic agent” refer to a compound, or a pharmaceutical composition thereof, which is administered to a subject for treating, preventing, or ameliorating one or more symptoms of a disorder or disease.

[0065] The term “release controlling excipient” refers to an excipient whose primary function is to modify the duration or place of release of the active substance from a dosage form as compared with a conventional immediate release dosage form.

[0066] The term “non-release controlling excipient” refers to an excipient whose primary function does not include modifying the duration or place of release of the active substance from a dosage form as compared with a conventional immediate release dosage form.

### **Compounds**

[0067] In some embodiments, provided herein is a compound of Formula (I) having the structure:



Formula (I);

wherein:

each  $R^1$  is independently halogen, -CN, -NO<sub>2</sub>, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -OC(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -N(R<sup>4</sup>)C(O)R<sup>3</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -N(R<sup>4</sup>)C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, -N(R<sup>4</sup>)S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>;

each  $R^2$  is independently C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each  $R^3$  is independently C<sub>1-6</sub>alkyl;

each  $R^4$  is independently H or C<sub>1-6</sub>alkyl;

each  $R^5$  and each  $R^6$  are independently H or C<sub>1-6</sub>alkyl; or  $R^5$  and  $R^6$  together with the nitrogen atom to which they are attached form an optionally substituted C<sub>1-6</sub>heterocycloalkyl;

p is 0, 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, or 4;

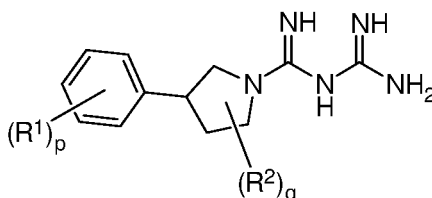
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

[0068] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>,

C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, -CO<sub>2</sub>R<sup>4</sup>, or -C(O)NR<sup>5</sup>R<sup>6</sup>. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -OR<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, or C<sub>1-6</sub>haloalkoxy. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -OR<sup>4</sup>, or C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -F or -Cl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -F. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -Cl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -OR<sup>4</sup>. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -OR<sup>4</sup> and R<sup>4</sup> is C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is -OCH<sub>3</sub>. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is -OH. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is -CH<sub>3</sub>. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is C<sub>1-6</sub>haloalkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is -CF<sub>3</sub>. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is C<sub>1-6</sub>haloalkoxy. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is -OCF<sub>3</sub>. In some embodiments is a compound of Formula (I), or a

pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 5. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 4. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 3. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 2. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 1. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 0. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is -CH<sub>3</sub>. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkoxy. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is -OCH<sub>3</sub>. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 4. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 3. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 2. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 1. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 0.

**[0069]** In some embodiments, provided herein is a compound of Formula (Ia) having the structure:



Formula (Ia);

wherein:

each R<sup>1</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl,

optionally substituted heteroaryl,  $-\text{C}(\text{O})\text{R}^3$ ,  $-\text{OC}(\text{O})\text{R}^3$ ,  $-\text{CO}_2\text{R}^4$ ,  $-\text{N}(\text{R}^4)\text{C}(\text{O})\text{R}^3$ ,  $-\text{C}(\text{O})\text{NR}^5\text{R}^6$ ,  $-\text{N}(\text{R}^4)\text{C}(\text{O})\text{NR}^5\text{R}^6$ ,  $-\text{S}(\text{O})_2\text{R}^3$ ,  $-\text{N}(\text{R}^4)\text{S}(\text{O})_2\text{R}^3$ , or  $-\text{S}(\text{O})_2\text{NR}^5\text{R}^6$ ;

each  $\text{R}^2$  is independently  $\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkoxy,  $\text{C}_{1-6}$ haloalkyl,  $\text{C}_{1-6}$ haloalkoxy, optionally substituted  $\text{C}_{1-6}$ heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each  $\text{R}^3$  is independently  $\text{C}_{1-6}$ alkyl;

each  $\text{R}^4$  is independently H or  $\text{C}_{1-6}$ alkyl;

each  $\text{R}^5$  and each  $\text{R}^6$  are independently H or  $\text{C}_{1-6}$ alkyl; or  $\text{R}^5$  and  $\text{R}^6$  together with the nitrogen atom to which they are attached form an optionally substituted  $\text{C}_{1-6}$ heterocycloalkyl;

p is 0, 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, or 4;

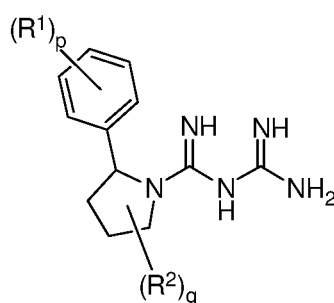
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

**[0070]** In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^1$  is independently halogen,  $-\text{OR}^4$ ,  $-\text{NR}^4\text{R}^4$ ,  $\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ haloalkyl,  $\text{C}_{1-6}$ haloalkoxy, optionally substituted  $\text{C}_{1-6}$ heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl,  $-\text{C}(\text{O})\text{R}^3$ ,  $-\text{CO}_2\text{R}^4$ ,  $-\text{C}(\text{O})\text{NR}^5\text{R}^6$ ,  $-\text{S}(\text{O})_2\text{R}^3$ , or  $-\text{S}(\text{O})_2\text{NR}^5\text{R}^6$ . In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^1$  is independently halogen,  $-\text{OR}^4$ ,  $-\text{NR}^4\text{R}^4$ ,  $\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ haloalkyl,  $\text{C}_{1-6}$ haloalkoxy,  $-\text{CO}_2\text{R}^4$ , or  $-\text{C}(\text{O})\text{NR}^5\text{R}^6$ . In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^1$  is independently halogen,  $-\text{OR}^4$ ,  $\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ haloalkyl, or  $\text{C}_{1-6}$ haloalkoxy. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^1$  is independently halogen,  $-\text{OR}^4$ , or  $\text{C}_{1-6}$ alkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^1$  is independently halogen. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^1$  is independently -F or -Cl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^1$  is independently -F. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^1$  is independently -Cl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^1$  is independently  $-\text{OR}^4$ . In some embodiments is a compound of Formula (Ia), or a

pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $-OR^4$  and  $R^4$  is  $C_{1-6}$ alkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-OCH_3$ . In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-OH$ . In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $C_{1-6}$ alkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-CH_3$ . In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $C_{1-6}$ haloalkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-CF_3$ . In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $C_{1-6}$ haloalkoxy. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-OCF_3$ . In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 5. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 4. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 3. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 2. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 1. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 0. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkyl or  $C_{1-6}$ alkoxy. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is  $-CH_3$ . In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkoxy. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is  $-OCH_3$ . In some embodiments is a compound of

Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 4. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 3. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 2. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 1. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 0.

**[0071]** In some embodiments, provided herein is a compound of Formula (Ib) having the structure:



Formula (Ib);

wherein:

each  $R^1$  is independently halogen, -CN, -NO<sub>2</sub>, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -OC(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -N(R<sup>4</sup>)C(O)R<sup>3</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -N(R<sup>4</sup>)C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, -N(R<sup>4</sup>)S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>;

each  $R^2$  is independently C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each  $R^3$  is independently C<sub>1-6</sub>alkyl;

each  $R^4$  is independently H or C<sub>1-6</sub>alkyl;

each  $R^5$  and each  $R^6$  are independently H or C<sub>1-6</sub>alkyl; or  $R^5$  and  $R^6$  together with the nitrogen atom to which they are attached form an optionally substituted C<sub>1-6</sub>heterocycloalkyl;

p is 0, 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

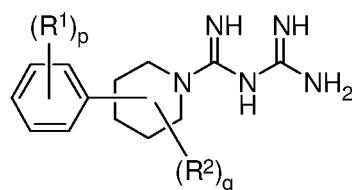
**[0072]** In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>,



C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, -CO<sub>2</sub>R<sup>4</sup>, or -C(O)NR<sup>5</sup>R<sup>6</sup>. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -OR<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, or C<sub>1-6</sub>haloalkoxy. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -OR<sup>4</sup>, or C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -F or -Cl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -F. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -Cl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -OR<sup>4</sup>. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -OR<sup>4</sup> and R<sup>4</sup> is C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is -OCH<sub>3</sub>. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is -OH. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is -CH<sub>3</sub>. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is C<sub>1-6</sub>haloalkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is -CF<sub>3</sub>. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is C<sub>1-6</sub>haloalkoxy. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is -OCF<sub>3</sub>. In some

embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 5. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 4. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 3. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 2. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 1. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 0. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is -CH<sub>3</sub>. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkoxy. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is -OCH<sub>3</sub>. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 4. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 3. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 2. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 1. In some embodiments is a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 0.

[0073] In some embodiments is a compound of Formula (II) having the structure:



Formula (II);

wherein:

each  $R^1$  is independently halogen, -CN, -NO<sub>2</sub>, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -OC(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -N(R<sup>4</sup>)C(O)R<sup>3</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -N(R<sup>4</sup>)C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, -N(R<sup>4</sup>)S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>;

each  $R^2$  is independently C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each  $R^3$  is independently C<sub>1-6</sub>alkyl;

each  $R^4$  is independently H or C<sub>1-6</sub>alkyl;

each  $R^5$  and each  $R^6$  are independently H or C<sub>1-6</sub>alkyl; or  $R^5$  and  $R^6$  together with the nitrogen atom to which they are attached form an optionally substituted C<sub>1-6</sub>heterocycloalkyl;

p is 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, or 4;

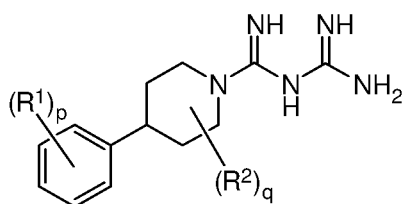
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

**[0074]** In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, -CO<sub>2</sub>R<sup>4</sup>, or -C(O)NR<sup>5</sup>R<sup>6</sup>. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen, -OR<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, or C<sub>1-6</sub>haloalkoxy. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen, -OR<sup>4</sup>, or C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently -F or -Cl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently -F. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently -Cl. In some embodiments is a compound of Formula

(II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $-OR^4$ . In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $-OR^4$  and  $R^4$  is  $C_{1-6}$ alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-OCH_3$ . In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-OH$ . In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $C_{1-6}$ alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-CH_3$ . In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $C_{1-6}$ haloalkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-CF_3$ . In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $C_{1-6}$ haloalkoxy. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-OCF_3$ . In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 5. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 4. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 3. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 2. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 1. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkyl or  $C_{1-6}$ alkoxy. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is  $-CH_3$ . In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkoxy. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is  $-OCH_3$ . In some embodiments is a

compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $q$  is 4. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $q$  is 3. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $q$  is 2. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $q$  is 1. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $q$  is 0.

**[0075]** In some embodiments is a compound of Formula (IIa) having the structure:



Formula (IIa);

wherein:

each  $R^1$  is independently halogen,  $-CN$ ,  $-NO_2$ ,  $-OR^4$ ,  $-NR^4R^4$ ,  $C_{1-6}$ alkyl,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy, optionally substituted  $C_{1-6}$ heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl,  $-C(O)R^3$ ,  $-OC(O)R^3$ ,  $-CO_2R^4$ ,  $-N(R^4)C(O)R^3$ ,  $-C(O)NR^5R^6$ ,  $-N(R^4)C(O)NR^5R^6$ ,  $-S(O)_2R^3$ ,  $-N(R^4)S(O)_2R^3$ , or  $-S(O)_2NR^5R^6$ ;

each  $R^2$  is independently  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy, optionally substituted  $C_{1-6}$ heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each  $R^3$  is independently  $C_{1-6}$ alkyl;

each  $R^4$  is independently H or  $C_{1-6}$ alkyl;

each  $R^5$  and each  $R^6$  are independently H or  $C_{1-6}$ alkyl; or  $R^5$  and  $R^6$  together with the nitrogen atom to which they are attached form an optionally substituted  $C_{1-6}$ heterocycloalkyl;

$p$  is 1, 2, 3, 4, or 5; and

$q$  is 0, 1, 2, 3, or 4;

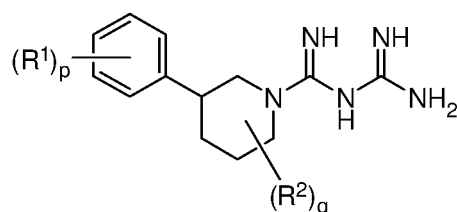
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

**[0076]** In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen,  $-OR^4$ ,  $-NR^4R^4$ ,  $C_{1-6}$ alkyl,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy, optionally substituted  $C_{1-6}$ heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl,  $-C(O)R^3$ ,  $-CO_2R^4$ ,  $-C(O)NR^5R^6$ ,  $-S(O)_2R^3$ , or -

$S(O)_2NR^5R^6$ . In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen,  $-OR^4$ ,  $-NR^4R^4$ ,  $C_{1-6}alkyl$ ,  $C_{1-6}haloalkyl$ ,  $C_{1-6}haloalkoxy$ ,  $-CO_2R^4$ , or  $-C(O)NR^5R^6$ . In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen,  $-OR^4$ ,  $C_{1-6}alkyl$ ,  $C_{1-6}haloalkyl$ , or  $C_{1-6}haloalkoxy$ . In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen,  $-OR^4$ , or  $C_{1-6}alkyl$ . In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $-F$  or  $-Cl$ . In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $-F$ . In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $-Cl$ . In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $-OR^4$ . In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $-OR^4$  and  $R^4$  is  $C_{1-6}alkyl$ . In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-OCH_3$ . In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-OH$ . In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $C_{1-6}alkyl$ . In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-CH_3$ . In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $C_{1-6}haloalkyl$ . In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-CF_3$ . In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $C_{1-6}haloalkoxy$ . In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-OCF_3$ . In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 5. In some embodiments is a compound of Formula

(IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 4. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 3. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 2. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 1. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is -CH<sub>3</sub>. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkoxy. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is -OCH<sub>3</sub>. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 4. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 3. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 2. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 1. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 0.

[0077] In some embodiments is a compound of Formula (IIb) having the structure:



Formula (IIb);

wherein:

each R<sup>1</sup> is independently halogen, -CN, -NO<sub>2</sub>, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -OC(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -N(R<sup>4</sup>)C(O)R<sup>3</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -N(R<sup>4</sup>)C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, -N(R<sup>4</sup>)S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>;

each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R<sup>3</sup> is independently C<sub>1-6</sub>alkyl;

each R<sup>4</sup> is independently H or C<sub>1-6</sub>alkyl;

each R<sup>5</sup> and each R<sup>6</sup> are independently H or C<sub>1-6</sub>alkyl; or R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form an optionally substituted C<sub>1-6</sub>heterocycloalkyl;

p is 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

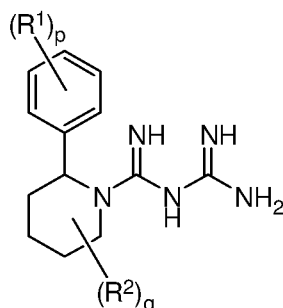
**[0078]** In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, -CO<sub>2</sub>R<sup>4</sup>, or -C(O)NR<sup>5</sup>R<sup>6</sup>. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -OR<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, or C<sub>1-6</sub>haloalkoxy. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -OR<sup>4</sup>, or C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -F or -Cl. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -F. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -Cl. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -OR<sup>4</sup>. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -OR<sup>4</sup> and R<sup>4</sup> is C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (IIb),



or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is -OCH<sub>3</sub>. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is -OH. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is -CH<sub>3</sub>. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is C<sub>1-6</sub>haloalkyl. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is -CF<sub>3</sub>. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is C<sub>1-6</sub>haloalkoxy. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is -OCF<sub>3</sub>. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 5. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 4. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 3. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 2. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 1. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is -CH<sub>3</sub>. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently C<sub>1-6</sub>alkoxy. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is -OCH<sub>3</sub>. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 4. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 3. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or

stereoisomer thereof, wherein each q is 2. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 1. In some embodiments is a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 0.

**[0079]** In some embodiments is a compound of Formula (IIc) having the structure:



Formula (IIc);

wherein:

each  $R^1$  is independently halogen,  $-CN$ ,  $-NO_2$ ,  $-OR^4$ ,  $-NR^4R^4$ ,  $C_{1-6}alkyl$ ,  $C_{1-6}haloalkyl$ ,  $C_{1-6}haloalkoxy$ , optionally substituted  $C_{1-6}heterocycloalkyl$ , optionally substituted aryl, optionally substituted heteroaryl,  $-C(O)R^3$ ,  $-OC(O)R^3$ ,  $-CO_2R^4$ ,  $-N(R^4)C(O)R^3$ ,  $-C(O)NR^5R^6$ ,  $-N(R^4)C(O)NR^5R^6$ ,  $-S(O)_2R^3$ ,  $-N(R^4)S(O)_2R^3$ , or  $-S(O)_2NR^5R^6$ ;

each  $R^2$  is independently  $C_{1-6}alkyl$ ,  $C_{1-6}alkoxy$ ,  $C_{1-6}haloalkyl$ ,  $C_{1-6}haloalkoxy$ , optionally substituted  $C_{1-6}heterocycloalkyl$ , optionally substituted aryl, or optionally substituted heteroaryl;

each  $R^3$  is independently  $C_{1-6}alkyl$ ;

each  $R^4$  is independently H or  $C_{1-6}alkyl$ ;

each  $R^5$  and each  $R^6$  are independently H or  $C_{1-6}alkyl$ ; or  $R^5$  and  $R^6$  together with the nitrogen atom to which they are attached form an optionally substituted  $C_{1-6}heterocycloalkyl$ ;

p is 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, or 4;

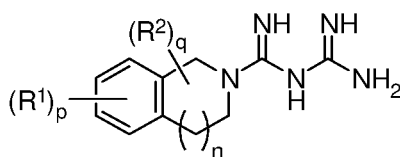
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

**[0080]** In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen,  $-OR^4$ ,  $-NR^4R^4$ ,  $C_{1-6}alkyl$ ,  $C_{1-6}haloalkyl$ ,  $C_{1-6}haloalkoxy$ , optionally substituted  $C_{1-6}heterocycloalkyl$ , optionally substituted aryl, optionally substituted heteroaryl,  $-C(O)R^3$ ,  $-CO_2R^4$ ,  $-C(O)NR^5R^6$ ,  $-S(O)_2R^3$ , or  $-S(O)_2NR^5R^6$ . In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen, -

OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, -CO<sub>2</sub>R<sup>4</sup>, or -C(O)NR<sup>5</sup>R<sup>6</sup>. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -OR<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, or C<sub>1-6</sub>haloalkoxy. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -OR<sup>4</sup>, or C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -F or -Cl. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -F. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -Cl. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -OR<sup>4</sup>. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -OR<sup>4</sup> and R<sup>4</sup> is C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is -OCH<sub>3</sub>. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is -OH. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is -CH<sub>3</sub>. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is C<sub>1-6</sub>haloalkyl. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is -CF<sub>3</sub>. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is C<sub>1-6</sub>haloalkoxy. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is -OCF<sub>3</sub>. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 5. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 4. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt,

solvate, or stereoisomer thereof, wherein each p is 3. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 2. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 1. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is -CH<sub>3</sub>. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkoxy. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is -OCH<sub>3</sub>. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 4. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 3. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 2. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 1. In some embodiments is a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 0.

**[0081]** In some embodiments is a compound having the structure of Formula (III):



Formula (III);

wherein:

each R<sup>1</sup> is independently halogen, -CN, -NO<sub>2</sub>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-</sub>

6haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -OC(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -N(R<sup>4</sup>)C(O)R<sup>3</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -N(R<sup>4</sup>)C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, -N(R<sup>4</sup>)S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>;

each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R<sup>3</sup> is independently C<sub>1-6</sub>alkyl;

each R<sup>4</sup> is independently H or C<sub>1-6</sub>alkyl;

each R<sup>5</sup> and each R<sup>6</sup> are independently H or C<sub>1-6</sub>alkyl; or R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form an optionally substituted C<sub>1-6</sub>heterocycloalkyl;

n is 0 or 1;

p is 1, 2, 3, or 4; and

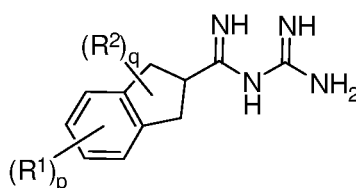
q is 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

**[0082]** In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, -CO<sub>2</sub>R<sup>4</sup>, or -C(O)NR<sup>5</sup>R<sup>6</sup>. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, or C<sub>1-6</sub>haloalkoxy. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen or C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -F or -Cl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -F. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -Cl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is -CH<sub>3</sub>. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is C<sub>1-6</sub>haloalkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer

thereof, wherein each  $R^1$  is  $-CF_3$ . In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $C_{1-6}$ haloalkoxy. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-OCF_3$ . In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 4. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 3. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 2. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 1. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkyl or  $C_{1-6}$ alkoxy. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is  $-CH_3$ . In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkoxy. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is  $-OCH_3$ . In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $q$  is 4. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $q$  is 3. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $q$  is 2. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $q$  is 1. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $q$  is 0. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $n$  is 0. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $n$  is 1.

**[0083]** In some embodiments is a compound having the structure of Formula (IIIa):



## Formula (IIIa);

wherein:

each R<sup>1</sup> is independently halogen, -CN, -NO<sub>2</sub>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -OC(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -N(R<sup>4</sup>)C(O)R<sup>3</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -N(R<sup>4</sup>)C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, -N(R<sup>4</sup>)S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>;

each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R<sup>3</sup> is independently C<sub>1-6</sub>alkyl;

each R<sup>4</sup> is independently H or C<sub>1-6</sub>alkyl;

each R<sup>5</sup> and each R<sup>6</sup> are independently H or C<sub>1-6</sub>alkyl; or R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form an optionally substituted C<sub>1-6</sub>heterocycloalkyl;

p is 1, 2, 3, or 4; and

q is 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

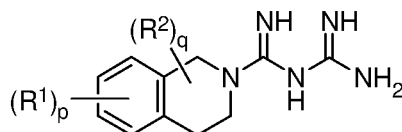
**[0084]** In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, -CO<sub>2</sub>R<sup>4</sup>, or -C(O)NR<sup>5</sup>R<sup>6</sup>. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, or C<sub>1-6</sub>haloalkoxy. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen or C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -F or -Cl. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently -F. In some embodiments is a

compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently -Cl. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $C_{1-6}$ alkyl. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is -CH<sub>3</sub>. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $C_{1-6}$ haloalkyl. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is -CF<sub>3</sub>. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $C_{1-6}$ haloalkoxy. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is -OCF<sub>3</sub>. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 4. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 3. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 2. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 1. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkyl or  $C_{1-6}$ alkoxy. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkyl. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is -CH<sub>3</sub>. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkoxy. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is -OCH<sub>3</sub>. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 4. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 3. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 2. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 1. In some embodiments is a compound of Formula



(IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 0.

**[0085]** In some embodiments is a compound having the structure of Formula (IIIb):



Formula (IIIb);

wherein:

each  $R^1$  is independently halogen, -CN, -NO<sub>2</sub>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-</sub>

<sub>6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -OC(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -N(R<sup>4</sup>)C(O)R<sup>3</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -N(R<sup>4</sup>)C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, -N(R<sup>4</sup>)S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>;

each  $R^2$  is independently C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each  $R^3$  is independently C<sub>1-6</sub>alkyl;

each  $R^4$  is independently H or C<sub>1-6</sub>alkyl;

each  $R^5$  and each  $R^6$  are independently H or C<sub>1-6</sub>alkyl; or  $R^5$  and  $R^6$  together with the nitrogen atom to which they are attached form an optionally substituted C<sub>1-</sub>

<sub>6</sub>heterocycloalkyl;

p is 1, 2, 3, or 4; and

q is 0, 1, 2, 3, or 4;

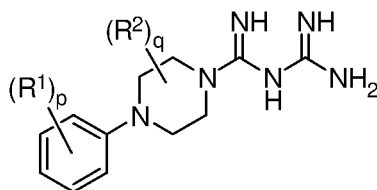
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

**[0086]** In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, -CO<sub>2</sub>R<sup>4</sup>, or -C(O)NR<sup>5</sup>R<sup>6</sup>. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, or C<sub>1-6</sub>haloalkoxy. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen or C<sub>1-6</sub>alkyl. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically

acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently -F or -Cl. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently -F. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently -Cl. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $C_{1-6}$ alkyl. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-CH_3$ . In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $C_{1-6}$ haloalkyl. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-CF_3$ . In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $C_{1-6}$ haloalkoxy. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-OCF_3$ . In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 4. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 3. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 2. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each p is 1. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkyl or  $C_{1-6}$ alkoxy. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkyl. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is  $-CH_3$ . In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkoxy. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is  $-OCH_3$ . In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein

each q is 4. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 3. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 2. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 1. In some embodiments is a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each q is 0.

**[0087]** In some embodiments is a compound having the structure of Formula (IV):



Formula (IV);

wherein:

each  $R^1$  is independently  $-CN$ ,  $-NR^4R^4$ ,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy, optionally substituted  $C_{1-6}$ heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl,  $-C(O)R^3$ ,  $-OC(O)R^3$ ,  $-CO_2R^4$ ,  $-N(R^4)C(O)R^3$ ,  $-C(O)NR^5R^6$ ,  $-N(R^4)C(O)NR^5R^6$ ,  $-S(O)_2R^3$ ,  $-N(R^4)S(O)_2R^3$ , or  $-S(O)_2NR^5R^6$ ;

each  $R^2$  is independently  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy, optionally substituted  $C_{1-6}$ heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each  $R^3$  is independently  $C_{1-6}$ alkyl;

each  $R^4$  is independently H or  $C_{1-6}$ alkyl;

each  $R^5$  and each  $R^6$  are independently H or  $C_{1-6}$ alkyl; or  $R^5$  and  $R^6$  together with the nitrogen atom to which they are attached form an optionally substituted  $C_{1-6}$ heterocycloalkyl;

p is 1, 2, 3, 4, or 5; and

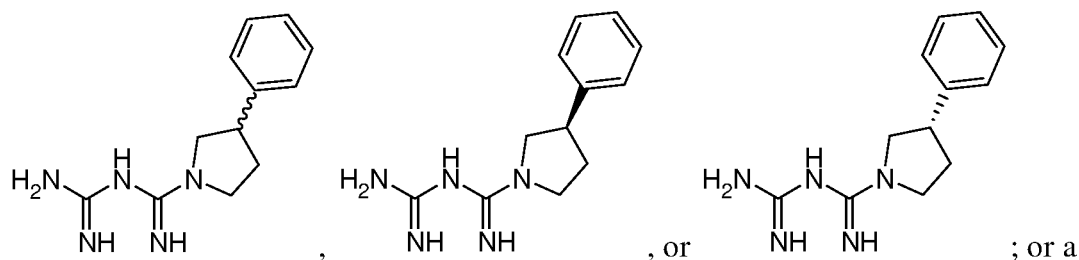
q is 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

**[0088]** In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $-NR^4R^4$ ,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy, optionally substituted  $C_{1-6}$ heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl,  $-C(O)R^3$ ,  $-CO_2R^4$ ,  $-C(O)NR^5R^6$ ,  $-S(O)_2R^3$ , or  $-S(O)_2NR^5R^6$ . In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $-NR^4R^4$ ,  $C_{1-6}$ haloalkyl,  $C_{1-6}$

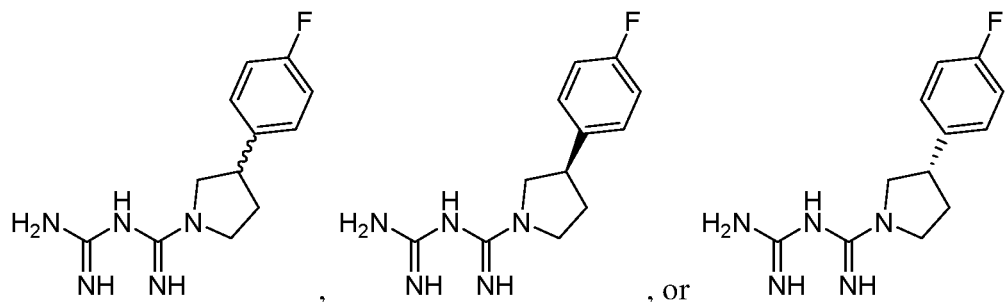
$_6$ haloalkoxy,  $-\text{CO}_2\text{R}^4$ , or  $-\text{C}(\text{O})\text{NR}^5\text{R}^6$ . In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^1$  is independently  $\text{C}_{1-6}$ haloalkyl or  $\text{C}_{1-6}$ haloalkoxy. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^1$  is independently  $\text{C}_{1-6}$ haloalkyl. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^1$  is  $-\text{CF}_3$ . In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^1$  is  $\text{C}_{1-6}$ haloalkoxy. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^1$  is  $-\text{OCF}_3$ . In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 1. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 2. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 3. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 4. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $p$  is 5. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^2$  is independently  $\text{C}_{1-6}$ alkyl or  $\text{C}_{1-6}$ alkoxy. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^2$  is independently  $\text{C}_{1-6}$ alkyl. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^2$  is  $-\text{CH}_3$ . In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^2$  is  $\text{C}_{1-6}$ alkoxy. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $\text{R}^2$  is  $-\text{OCH}_3$ . In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $q$  is 2. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $q$  is 1. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $q$  is 0.

**[0089]** In some embodiments is a compound having the structure:



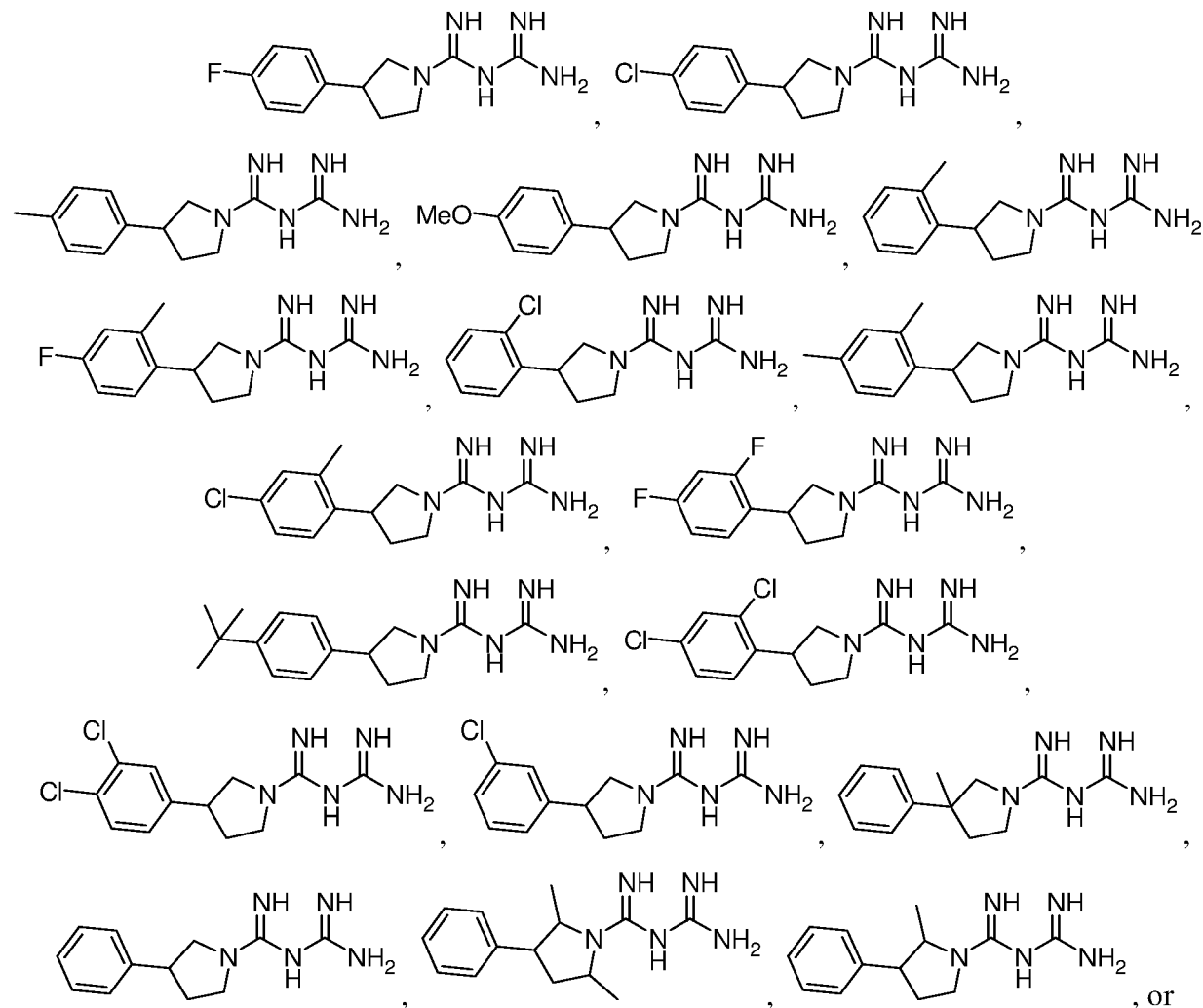
pharmaceutically acceptable salt or solvate thereof.

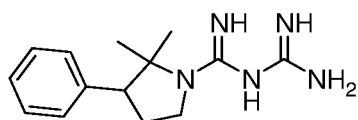
[0090] In some embodiments is a compound having the structure:



or a pharmaceutically acceptable salt or solvate thereof.

[0091] In some embodiments is a compound having the structure:





; or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

**[0092]** Any combination of the groups described above for the various variables is contemplated herein.

**[0093]** Throughout the specification, groups and substituents thereof can be chosen to provide stable moieties and compounds.

### **Further Forms of Compounds**

**[0094]** In some embodiments, the compounds of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV) described herein may exist as diastereomers, enantiomers, or other stereoisomeric forms. The compounds of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV) presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Separation of stereoisomers may be performed by chromatography or by the forming diastereomeric and separation by recrystallization, or chromatography, or any combination thereof. (Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981, herein incorporated by reference for this disclosure). Stereoisomers may also be obtained by stereoselective synthesis.

**[0095]** In some embodiments, compounds of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV) may exist as tautomers. All tautomers are included within the formulas described herein.

**[0096]** In some embodiments, the compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV) is provided as a pharmaceutically acceptable salt (*See*, Berge et al., *J. Pharm. Sci.* **1977**, 66, 1-19; and "Handbook of Pharmaceutical Salts, Properties, and Use," Stah and Wermuth, Ed.; Wiley-VCH and VHCA, Zurich, 2002).

**[0097]** Suitable acids for use in the preparation of pharmaceutically acceptable salts include, but are not limited to, acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, boric acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, cyclohexanesulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid,  $\alpha$ -oxo-glutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, (+)-L-lactic

acid, (±)-DL-lactic acid, lactobionic acid, lauric acid, maleic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, perchloric acid, phosphoric acid, L-pyroglutamic acid, saccharic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, undecylenic acid, and valeric acid.

**[0098]** In some embodiments, the compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV) is provided as a prodrug, which is a functional derivative of the compound of Formula (I) or Formula (II) and is readily convertible into the parent compound in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent compound. They may, for instance, be bioavailable by oral administration whereas the parent compound is not. The prodrug may also have enhanced solubility in pharmaceutical compositions over the parent compound. A prodrug may be converted into the parent drug by various mechanisms, including enzymatic processes and metabolic hydrolysis. See Harper, *Progress in Drug Research* **1962**, *4*, 221-294; Morozowich et al. in "Design of Biopharmaceutical Properties through Prodrugs and Analogs," Roche Ed., APHA Acad. Pharm. Sci. 1977; "Bioreversible Carriers in Drug in Drug Design, Theory and Application," Roche Ed., APHA Acad. Pharm. Sci. 1987; "Design of Prodrugs," Bundgaard, Elsevier, 1985; Wang et al., *Curr. Pharm. Design* 1999, *5*, 265-287; Pauletti et al., *Adv. Drug. Delivery Rev.* **1997**, *27*, 235-256; Mizen et al., *Pharm. Biotech.* **1998**, *11*, 345-365; Gaignault et al., *Pract. Med. Chem.* **1996**, 671-696; Asgharnejad in "Transport Processes in Pharmaceutical Systems," Amidon et al., Ed., Marcell Dekker, 185-218, 2000; Balant et al., *Eur. J. Drug Metab. Pharmacokinet.* **1990**, *15*, 143-53; Balimane and Sinko, *Adv. Drug Delivery Rev.* **1999**, *39*, 183-209; Browne, *Clin. Neuropharmacol.* **1997**, *20*, 1-12; Bundgaard, *Arch. Pharm. Chem.* **1979**, *86*, 1-39; Bundgaard, *Controlled Drug Delivery* **1987**, *17*, 179-96; Bundgaard, *Adv. Drug Delivery Rev.* **1992**, *8*, 1-38; Fleisher et al., *Adv. Drug Delivery Rev.* **1996**, *19*, 115-130; Fleisher et al., *Methods Enzymol.* **1985**, *112*, 360-381; Farquhar et al., *J. Pharm. Sci.* **1983**, *72*, 324-325; Freeman et al., *J. Chem. Soc., Chem. Commun.* **1991**, 875-877; Friis and Bundgaard, *Eur. J. Pharm. Sci.* **1996**, *4*, 49-59; Gangwar et al., *Des. Biopharm. Prop. Prodrugs Analogs*, **1977**, 409-421; Nathwani and Wood, *Drugs* **1993**, *45*, 866-94; Sinhababu and Thakker, *Adv. Drug Delivery Rev.* **1996**, *19*, 241-273; Stella et al., *Drugs* **1985**, *29*, 455-73; Tan et al., *Adv. Drug Delivery Rev.* **1999**, *39*, 117-151; Taylor, *Adv. Drug Delivery Rev.* **1996**, *19*, 131-148; Valentino and Borchardt, *Drug Discovery*

*Today* **1997**, 2, 148-155; Wiebe and Knaus, *Adv. Drug Delivery Rev.* **1999**, 39, 63-80; Waller et al., *Br. J. Clin. Pharmac.* **1989**, 28, 497-507.

**[0099]** In some embodiments, the compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV) described herein may be labeled isotopically (e.g. with a radioisotope) or by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, photoactivatable or chemiluminescent labels. Thus, in certain embodiments, the compounds of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV) described herein include isotopically-labeled compounds, which are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine and chlorine, such as, for example,  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{17}\text{O}$ ,  $^{35}\text{S}$ ,  $^{18}\text{F}$ ,  $^{36}\text{Cl}$ , respectively. In some embodiments, the deuterated compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV) also contains less prevalent isotopes for other elements, including, but not limited to,  $^{13}\text{C}$  or  $^{14}\text{C}$  for carbon and  $^{15}\text{N}$  for nitrogen.

**[00100]** In some embodiments, the deuterated compounds provided herein maintain the beneficial aspects of the corresponding non-isotopically enriched molecules while substantially decreasing toxicity (reducing the risk of lactic acidosis), increasing the half-life ( $T_{1/2}$ ), lowering the maximum plasma concentration ( $C_{\text{max}}$ ) of the minimum efficacious dose (MED), lowering the efficacious dose and thus decreasing the non-mechanism-related toxicity, and/or lowering the probability of drug-drug interactions.

### **Synthesis of Compounds**

**[00101]** In some embodiments, the synthesis of compounds described herein are accomplished using means described in the chemical literature, using the methods described herein, or by a combination thereof. In addition, solvents, temperatures and other reaction conditions presented herein may vary.

**[00102]** In other embodiments, the starting materials and reagents used for the synthesis of the compounds described herein are synthesized or are obtained from commercial sources, such as, but not limited to, Sigma-Aldrich, Fischer Scientific (Fischer Chemicals), and Acros Organics.

**[00103]** In further embodiments, the compounds described herein, and other related compounds having different substituents are synthesized using techniques and materials described herein as well as those that are recognized in the field, such as described, for example, in Fieser and



Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989), March, ADVANCED ORGANIC CHEMISTRY 4<sup>th</sup> Ed., (Wiley 1992); Carey and Sundberg, ADVANCED ORGANIC CHEMISTRY 4<sup>th</sup> Ed., Vols. A and B (Plenum 2000, 2001), and Green and Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 3<sup>rd</sup> Ed., (Wiley 1999) (all of which are incorporated by reference for such disclosure). General methods for the preparation of compound as disclosed herein may be derived from reactions and the reactions may be modified by the use of appropriate reagents and conditions, for the introduction of the various moieties found in the formulae as provided herein.

### **Pharmaceutical Compositions and Methods of Administration**

**[00104]** In some embodiments, provided herein is a pharmaceutical composition comprising a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient. In some embodiments, provided herein is a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient. In some embodiments, provided herein is a pharmaceutical composition comprising a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient. In some embodiments, provided herein is a pharmaceutical composition comprising a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient. In some embodiments, provided herein is a pharmaceutical composition comprising a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient. In some embodiments, provided herein is a pharmaceutical composition comprising a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient. In some embodiments, provided herein is a pharmaceutical composition comprising a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient. In some embodiments, provided herein is a pharmaceutical composition comprising a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient. In some embodiments, provided herein is a

pharmaceutical composition comprising a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient. In some embodiments, provided herein is a pharmaceutical composition comprising a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient. In some embodiments, provided herein is a pharmaceutical composition comprising a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient. In some embodiments, provided herein is a pharmaceutical composition comprising a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient.

**[00105]** In some embodiments, provided herein is a pharmaceutical composition in modified release dosage forms, comprising a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and one or more release controlling excipients as described herein. Suitable modified release dosage vehicles include, but are not limited to, hydrophilic or hydrophobic matrix devices, water-soluble separating layer coatings, enteric coatings, osmotic devices, multi-particulate devices, and combinations thereof. In some embodiments, the pharmaceutical compositions also comprise non-release controlling excipients.

**[00106]** In some embodiments, provided herein is a pharmaceutical composition in enteric coated dosage forms, comprising a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and one or more release controlling excipients for use in an enteric coated dosage form. In some embodiments, the pharmaceutical compositions also comprise non-release controlling excipients.

**[00107]** In some embodiments, provided herein is a pharmaceutical composition in effervescent dosage forms, comprising a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and one or more release controlling excipients for use in an enteric coated dosage form. In some embodiments, the pharmaceutical compositions also comprise non-release controlling excipients.

**[00108]** In some embodiments, provided herein is a pharmaceutical composition in a dosage form that has an instant releasing component and at least one delayed releasing component, and is capable of giving a discontinuous release of the compound in the form of at least two consecutive pulses separated in time from 0.1 up to 24 hours. The pharmaceutical compositions

comprise a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and one or more release controlling and non-release controlling excipients, such as those excipients suitable for a disruptable semi-permeable membrane and as swellable substances.

**[00109]** In some embodiments, provided herein is a pharmaceutical composition in a dosage form for oral administration to a subject, comprising a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and one or more pharmaceutically acceptable excipients or carriers, enclosed in an intermediate reactive layer comprising a gastric juice-resistant polymeric layered material partially neutralized with alkali and having cation exchange capacity and a gastric juice-resistant outer layer.

**[00110]** In some embodiments, provided herein are pharmaceutical compositions comprising about 0.1 to about 100 mg, about 0.5 to about 50 mg, about 1 to about 20 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 10 mg, about 15 mg, about 20 mg of one or more compounds of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV) in the form of tablets for oral administration. In some embodiments, the pharmaceutical compositions further comprise hydroxypropyl methylcellulose, lactose, magnesium stearate, micro-crystalline cellulose, polyethylene glycol, sodium starch glycolate, titanium dioxide, and polysorbate 80.

**[00111]** In some embodiments, provided herein are pharmaceutical compositions comprising about 0.1 to about 100 mg, about 0.5 to about 50 mg, about 1 to about 20 mg, about 1 mg, about 2 mg, about 3 mg, about 4mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 10 mg, about 15 mg, about 20 mg of one or more compounds of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV) in the form of coated two-layer tablet for oral administration: one layer that releases a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV) immediately and another layer that allows a slower release of additional compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV). In some embodiments, the pharmaceutical compositions further comprise colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, sodium starch glycolate, and titanium dioxide.

**[00112]** In some embodiments, the pharmaceutical compositions provided herein are provided in unit-dosage forms or multiple-dosage forms. Unit-dosage forms, as used herein, refer to physically discrete units suitable for administration to human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the

active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of unit-dosage forms include ampules, syringes, and individually packaged tablets and capsules. Unit-dosage forms may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of multiple-dosage forms include vials, bottles of tablets or capsules, or bottles of pints or gallons.

**[00113]** In some embodiments, the compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV) provided herein is administered alone, or in combination with one or more other compounds provided herein, or one or more other active ingredients. In some embodiments, the pharmaceutical compositions that comprise a compound provided herein are formulated in various dosage forms for oral, parenteral, and topical administration. In some embodiments, the pharmaceutical compositions are also formulated as a modified release dosage form, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Delivery Technology*, Rathbone et al., Eds., *Drugs and the Pharmaceutical Science*, Marcel Dekker, Inc.: New York, NY, 2002; Vol. 126).

**[00114]** The pharmaceutical compositions provided herein may be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

**[00115]** In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds may be administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

**[00116]** In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the compounds may be given continuously or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday").

[00117] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. Patients can, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

#### **A. Oral Administration**

[00118] In some embodiments, the pharmaceutical compositions provided herein are provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, capsules, pills, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, granules, bulk powders, effervescent or non-effervescent powders or granules, solutions, emulsions, suspensions, solutions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions may contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, and flavoring agents.

[00119] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remains intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, Panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. In some embodiments, the binder or filler is present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

[00120] Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when

present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets.

**[00121]** Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrillin potassium; starches, such as corn starch, potato starch, tapioca starch, and pregelatinized starch; clays; aligins; and mixtures thereof. The amount of disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

**[00122]** Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL<sup>®</sup> 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL<sup>®</sup> (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

**[00123]** Suitable glidants include colloidal silicon dioxide, CAB-O-SIL<sup>®</sup> (Cabot Co. of Boston, MA), and asbestos-free talc. Coloring agents include any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Flavoring agents include natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Sweetening agents include sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN<sup>®</sup> 20), polyoxyethylene sorbitan monooleate 80 (TWEEN<sup>®</sup> 80), and triethanolamine oleate. Suspending and dispersing agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum,

acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Preservatives include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Solvents include glycerin, sorbitol, ethyl alcohol, and syrup. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate.

**[00124]** It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

**[00125]** In some embodiments, the pharmaceutical compositions provided herein are provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenylsalicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

**[00126]** In some embodiments, the tablet dosage forms are prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

**[00127]** In some embodiments, the pharmaceutical compositions provided herein are provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the

addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. In some embodiments, the liquid, semisolid, and solid dosage forms provided herein are encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

**[00128]** In some embodiments, the pharmaceutical compositions provided herein are provided in liquid and semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion is a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions may include a pharmaceutically acceptable non-aqueous liquids or solvent, emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically acceptable acetal, such as a di(lower alkyl) acetal of a lower alkyl aldehyde (the term "lower" means an alkyl having between 1 and 6 carbon atoms), e.g., acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs are clear, sweetened, and hydroalcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, e.g., water, to be measured conveniently for administration.

**[00129]** Other useful liquid and semisolid dosage forms include, but are not limited to, those containing the active ingredient(s) provided herein, and a dialkylated mono- or poly-alkylene glycol, including, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether, wherein 350, 550, and 750 refer to the approximate average molecular weight of the polyethylene glycol. These formulations may further comprise one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, bisulfite, sodium metabisulfite, thiodipropionic acid and its esters, and dithiocarbamates.



[00130] In some embodiments, the pharmaceutical compositions provided herein for oral administration are provided in the forms of liposomes, micelles, microspheres, or nanosystems. Micellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

[00131] In some embodiments, the pharmaceutical compositions provided herein are provided as non-effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.

[00132] Coloring and flavoring agents can be used in all of the above dosage forms.

[00133] In some embodiments, the pharmaceutical compositions provided herein are formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[00134] In some embodiments, the pharmaceutical compositions provided herein are co-formulated with other active ingredients which do not impair the desired therapeutic action, or with substances that supplement the desired action, such as other GABA<sub>A</sub> receptor modulators.

#### **B. Parenteral Administration**

[00135] In some embodiments, the pharmaceutical compositions provided herein are administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, and subcutaneous administration.

[00136] In some embodiments, the pharmaceutical compositions provided herein are formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (*see, Remington: The Science and Practice of Pharmacy, supra*).

[00137] The pharmaceutical compositions intended for parenteral administration may include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents,

wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

**[00138]** Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methyl-2-pyrrolidone, dimethylacetamide, and dimethylsulfoxide.

**[00139]** Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl *p*-hydroxybenzates, thimerosal, benzalkonium chloride, benzethonium chloride, methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents include those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including  $\alpha$ -cyclodextrin,  $\beta$ -cyclodextrin, hydroxypropyl- $\beta$ -cyclodextrin, sulfobutylether- $\beta$ -cyclodextrin, and sulfobutylether 7- $\beta$ -cyclodextrin (CAPTISOL<sup>®</sup>, CyDex, Lenexa, KS).

**[00140]** In some embodiments, the pharmaceutical compositions provided herein are formulated for single or multiple dosage administration. The single dosage formulations are packaged in an ampule, a vial, or a syringe. The multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungistatic concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

[00141] In one embodiment, the pharmaceutical compositions are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

[00142] In some embodiments, the pharmaceutical compositions provided herein are formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[00143] In some embodiments, the pharmaceutical compositions are formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

[00144] Suitable inner matrixes include polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

[00145] Suitable outer polymeric membranes include polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

### **C. Topical Administration**

[00146] In some embodiments, the pharmaceutical compositions provided herein are administered topically to the skin, orifices, or mucosa. The topical administration, as used

herein, include (intra)dermal, conjunctival, intracorneal, intraocular, ophthalmic, auricular, transdermal, nasal, vaginal, urethral, respiratory, and rectal administration.

**[00147]** In some embodiments, the pharmaceutical compositions provided herein are formulated in any dosage forms that are suitable for topical administration for local or systemic effect, including emulsions, solutions, suspensions, creams, gels, hydrogels, ointments, dusting powders, dressings, elixirs, lotions, suspensions, tinctures, pastes, foams, films, aerosols, irrigations, sprays, suppositories, bandages, dermal patches. The topical formulation of the pharmaceutical compositions provided herein may also comprise liposomes, micelles, microspheres, nanosystems, and mixtures thereof.

**[00148]** Pharmaceutically acceptable carriers and excipients suitable for use in the topical formulations provided herein include, but are not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, penetration enhancers, cryoprotectants, lyoprotectants, thickening agents, and inert gases.

**[00149]** The pharmaceutical compositions may also be administered topically by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free injection, such as POWDERJECT™ (Novartis AG, Basel, Switzerland), and BIOJECT™ (Bioject Medical Technologies Inc., Tualatin, OR).

**[00150]** In some embodiments, the pharmaceutical compositions provided herein are provided in the forms of ointments, creams, and gels. Suitable ointment vehicles include oleaginous or hydrocarbon vehicles, including such as lard, benzoinated lard, olive oil, cottonseed oil, and other oils, white petrolatum; emulsifiable or absorption vehicles, such as hydrophilic petrolatum, hydroxystearin sulfate, and anhydrous lanolin; water-removable vehicles, such as hydrophilic ointment; water-soluble ointment vehicles, including polyethylene glycols of varying molecular weight; emulsion vehicles, either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, including cetyl alcohol, glyceryl monostearate, lanolin, and stearic acid (*see, Remington: The Science and Practice of Pharmacy, supra*). These vehicles are emollient but generally require addition of antioxidants and preservatives.

**[00151]** Suitable cream base can be oil-in-water or water-in-oil. Cream vehicles may be water-washable, and contain an oil phase, an emulsifier, and an aqueous phase. The oil phase is also called the “internal” phase, which is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil

phase in volume, and generally contains a humectant. In some embodiments, the emulsifier in a cream formulation is a nonionic, anionic, cationic, or amphoteric surfactant.

**[00152]** Gels are semisolid, suspension-type systems. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the liquid carrier. Suitable gelling agents include crosslinked acrylic acid polymers, such as carbomers, carboxypolyalkylenes, Carbopol®; hydrophilic polymers, such as polyethylene oxides, polyoxyethylene-polyoxypropylene copolymers, and polyvinylalcohol; cellulosic polymers, such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and methylcellulose; gums, such as tragacanth and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing, and/or stirring.

**[00153]** In some embodiments, the pharmaceutical compositions provided herein are administered rectally, urethrally, vaginally, or perivaginally in the forms of suppositories, pessaries, bougies, poultices or cataplasm, pastes, powders, dressings, creams, plasters, contraceptives, ointments, solutions, emulsions, suspensions, tampons, gels, foams, sprays, or enemas. These dosage forms can be manufactured using conventional processes as described in *Remington: The Science and Practice of Pharmacy*, supra.

**[00154]** Rectal, urethral, and vaginal suppositories are solid bodies for insertion into body orifices, which are solid at ordinary temperatures but melt or soften at body temperature to release the active ingredient(s) inside the orifices. Pharmaceutically acceptable carriers utilized in rectal and vaginal suppositories include bases or vehicles, such as stiffening agents, which produce a melting point in the proximity of body temperature, when formulated with the pharmaceutical compositions provided herein; and antioxidants as described herein, including bisulfite and sodium metabisulfite. Suitable vehicles include, but are not limited to, cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol), spermaceti, paraffin, white and yellow wax, and appropriate mixtures of mono-, di- and triglycerides of fatty acids, hydrogels, such as polyvinyl alcohol, hydroxyethyl methacrylate, polyacrylic acid; glycerinated gelatin. In some embodiments, combinations of the various vehicles may be used. In some embodiments, rectal and vaginal suppositories are prepared by the compressed method or molding. The typical weight of a rectal and vaginal suppository is about 2 to about 3 g.

**[00155]** In some embodiments, the pharmaceutical compositions provided herein are administered ophthalmically in the forms of solutions, suspensions, ointments, emulsions, gel-forming solutions, powders for solutions, gels, ocular inserts, and implants.

**[00156]** In some embodiments, the pharmaceutical compositions provided herein are administered intranasally or by inhalation to the respiratory tract. In some embodiments, the pharmaceutical compositions are provided in the form of an aerosol or solution for delivery using a pressurized container, pump, spray, atomizer, such as an atomizer using electrohydrodynamics to produce a fine mist, or nebulizer, alone or in combination with a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. In some embodiments, the pharmaceutical compositions are provided as a dry powder for insufflation, alone or in combination with an inert carrier such as lactose or phospholipids; and nasal drops. For intranasal use, the powder may comprise a bioadhesive agent, including chitosan or cyclodextrin.

**[00157]** In some embodiments, solutions or suspensions for use in a pressurized container, pump, spray, atomizer, or nebulizer are formulated to contain ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active ingredient provided herein, a propellant as solvent; and/or a surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

**[00158]** In some embodiments, the pharmaceutical compositions provided herein are micronized to a size suitable for delivery by inhalation, such as about 50 micrometers or less, or about 10 micrometers or less. In some embodiments, particles of such sizes are prepared using a comminuting method known to those skilled in the art, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

**[00159]** In some embodiments, capsules, blisters and cartridges for use in an inhaler or insufflator are formulated to contain a powder mix of the pharmaceutical compositions provided herein; a suitable powder base, such as lactose or starch; and a performance modifier, such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose, and trehalose. The pharmaceutical compositions provided herein for inhaled/intranasal administration may further comprise a suitable flavor, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium.

**[00160]** In some embodiments, the pharmaceutical compositions provided herein for topical administration are formulated to be immediate release or modified release, including delayed-, sustained-, pulsed-, controlled-, targeted, and programmed release.

## D. Modified Release

**[00161]** In some embodiments, the pharmaceutical compositions provided herein are formulated as a modified release dosage form. As used herein, the term “modified release” refers to a dosage form in which the rate or place of release of the active ingredient(s) is different from that of an immediate dosage form when administered by the same route. Modified release dosage forms include delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. The pharmaceutical compositions in modified release dosage forms can be prepared using a variety of modified release devices and methods known to those skilled in the art, including, but not limited to, matrix controlled release devices, osmotic controlled release devices, multiparticulate controlled release devices, ion-exchange resins, enteric coatings, multilayered coatings, microspheres, liposomes, and combinations thereof. The release rate of the active ingredient(s) can also be modified by varying the particle sizes and polymorphism of the active ingredient(s).

**[00162]** Examples of modified release include, but are not limited to, those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; and 6,699,500.

### 1. Matrix-Controlled Release Devices

**[00163]** In some embodiments, the pharmaceutical compositions provided herein in a modified release dosage form are fabricated using a matrix-controlled release device known to those skilled in the art (*see*, Takada et al in “Encyclopedia of Controlled Drug Delivery,” Vol. 2, Mathiowitz ed., Wiley, 1999).

**[00164]** In one embodiment, the pharmaceutical compositions provided herein in a modified release dosage form is formulated using an erodible matrix device, which is water-swallowable, erodible, or soluble polymers, including synthetic polymers, and naturally occurring polymers and derivatives, such as polysaccharides and proteins.

**[00165]** Materials useful in forming an erodible matrix include, but are not limited to, chitin, chitosan, dextran, and pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum, and scleroglucan; starches, such as dextrin and maltodextrin; hydrophilic colloids, such as pectin; phosphatides, such as lecithin; alginates; propylene glycol alginate; gelatin; collagen; and celluloses, such as ethyl cellulose

(EC), methylethyl cellulose (MEC), carboxymethyl cellulose (CMC), CMEC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), and ethylhydroxy ethylcellulose (EHEC); polyvinyl pyrrolidone; polyvinyl alcohol; polyvinyl acetate; glycerol fatty acid esters; polyacrylamide; polyacrylic acid; copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT<sup>®</sup>, Rohm America, Inc., Piscataway, NJ); poly(2-hydroxyethyl-methacrylate); polylactides; copolymers of L-glutamic acid and ethyl-L-glutamate; degradable lactic acid-glycolic acid copolymers; poly-D-(-)-3-hydroxybutyric acid; and other acrylic acid derivatives, such as homopolymers and copolymers of butylmethacrylate, methylmethacrylate, ethylmethacrylate, ethylacrylate, (2-dimethylaminoethyl)methacrylate, and (trimethylaminoethyl)methacrylate chloride.

**[00166]** In further embodiments, the pharmaceutical compositions are formulated with a non-erodible matrix device. The active ingredient(s) is dissolved or dispersed in an inert matrix and is released primarily by diffusion through the inert matrix once administered. Materials suitable for use as a non-erodible matrix device included, but are not limited to, insoluble plastics, such as polyethylene, polypropylene, polyisoprene, polyisobutylene, polybutadiene, polymethylmethacrylate, polybutylmethacrylate, chlorinated polyethylene, polyvinylchloride, methyl acrylate-methyl methacrylate copolymers, ethylene-vinylacetate copolymers, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, ethylene/vinylalcohol copolymer, polyvinyl chloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, silicone rubbers, polydimethylsiloxanes, and silicone carbonate copolymers; hydrophilic polymers, such as ethyl cellulose, cellulose acetate, crospovidone, and cross-linked partially hydrolyzed polyvinyl acetate; and fatty compounds, such as carnauba wax, microcrystalline wax, and triglycerides.

**[00167]** In a matrix-controlled release system, the desired release kinetics can be controlled, for example, via the polymer type employed, the polymer viscosity, the particle sizes of the polymer and/or the active ingredient(s), the ratio of the active ingredient(s) versus the polymer, and other excipients in the compositions.

**[00168]** In some embodiments, the pharmaceutical compositions provided herein in a modified release dosage form are prepared by methods known to those skilled in the art, including direct



compression, dry or wet granulation followed by compression, melt-granulation followed by compression.

## 2. Osmotic Controlled-Release Devices

**[00169]** In some embodiments, the pharmaceutical compositions provided herein in a modified release dosage form are fabricated using an osmotic controlled-release device, including one-chamber system, two-chamber system, asymmetric membrane technology (AMT), and extruding core system (ECS). In general, such devices have at least two components: (a) the core which contains the active ingredient(s); and (b) a semipermeable membrane with at least one delivery port, which encapsulates the core. The semipermeable membrane controls the influx of water to the core from an aqueous environment of use so as to cause drug release by extrusion through the delivery port(s).

**[00170]** In addition to the active ingredient(s), the core of the osmotic device optionally includes an osmotic agent, which creates a driving force for transport of water from the environment of use into the core of the device. One class of osmotic agents water-swelling hydrophilic polymers, which are also referred to as “osmopolymers” and “hydrogels,” including, but not limited to, hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP), crosslinked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers, PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate and vinyl acetate, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolate.

**[00171]** The other class of osmotic agents are osmogens, which are capable of imbibing water to affect an osmotic pressure gradient across the barrier of the surrounding coating. Suitable osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphates, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol; organic acids, such as ascorbic acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid, edetic acid, glutamic acid, p-toluenesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

**[00172]** In some embodiments, osmotic agents of different dissolution rates are employed to influence how rapidly the active ingredient(s) is initially delivered from the dosage form. For example, amorphous sugars, such as Mannogeme EZ (SPI Pharma, Lewes, DE) can be used to provide faster delivery during the first couple of hours to promptly produce the desired therapeutic effect, and gradually and continually release of the remaining amount to maintain the desired level of therapeutic or prophylactic effect over an extended period of time. In this case, the active ingredient(s) is released at such a rate to replace the amount of the active ingredient metabolized and excreted.

**[00173]** The core may also include a wide variety of other excipients and carriers as described herein to enhance the performance of the dosage form or to promote stability or processing.

**[00174]** Materials useful in forming the semipermeable membrane include various grades of acrylics, vinyls, ethers, polyamides, polyesters, and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration, such as crosslinking. Examples of suitable polymers useful in forming the coating, include plasticized, unplasticized, and reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose triacetate,  $\beta$  glucan acetate,  $\beta$  glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxylated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCAT, poly(acrylic) acids and esters and poly-(methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

**[00175]** Semipermeable membrane may also be a hydrophobic microporous membrane, wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed in U.S. Pat. No. 5,798,119. Such hydrophobic but water-vapor permeable membrane are typically composed of hydrophobic polymers such as polyalkenes, polyethylene, polypropylene, polytetrafluoroethylene, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinylidene fluoride, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00176] In some embodiments, the delivery port(s) on the semipermeable membrane is formed post-coating by mechanical or laser drilling. In some embodiments, the delivery port(s) is formed in situ by erosion of a plug of water-soluble material or by rupture of a thinner portion of the membrane over an indentation in the core. In some embodiments, the delivery port(s) is formed during coating process, as in the case of asymmetric membrane coatings of the type disclosed in U.S. Pat. Nos. 5,612,059 and 5,698,220.

[00177] The total amount of the active ingredient(s) released and the release rate can substantially be modulated via the thickness and porosity of the semipermeable membrane, the composition of the core, and the number, size, and position of the delivery ports.

[00178] The pharmaceutical compositions in an osmotic controlled-release dosage form may further comprise additional conventional excipients as described herein to promote performance or processing of the formulation.

[00179] The osmotic controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; Santus and Baker, *J. Controlled Release* **1995**, 35, 1-21; Verma et al., *Drug Development and Industrial Pharmacy* **2000**, 26, 695-708; Verma et al., *J. Controlled Release* **2002**, 79, 7-27).

[00180] In certain embodiments, the pharmaceutical compositions provided herein are formulated as AMT controlled-release dosage form, which comprises an asymmetric osmotic membrane that coats a core comprising the active ingredient(s) and other pharmaceutically acceptable excipients. *See*, U.S. Pat. No. 5,612,059 and WO 2002/17918. The AMT controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art, including direct compression, dry granulation, wet granulation, and a dip-coating method.

[00181] In certain embodiments, the pharmaceutical compositions provided herein are formulated as ESC controlled-release dosage form, which comprises an osmotic membrane that coats a core comprising the active ingredient(s), a hydroxyethyl cellulose, and other pharmaceutically acceptable excipients.

### 3. Multiparticulate Controlled-Release Devices

[00182] In some embodiments, the pharmaceutical compositions provided herein in a modified release dosage form are fabricated a multiparticulate controlled-release device, which comprises a multiplicity of particles, granules, or pellets, ranging from about 10  $\mu\text{m}$  to about 3 mm, about 50  $\mu\text{m}$  to about 2.5 mm, or from about 100  $\mu\text{m}$  to about 1 mm in diameter. Such multiparticulates may be made by the processes known to those skilled in the art, including wet-

and dry-granulation, extrusion/spheronization, roller-compactation, melt-congealing, and by spray-coating seed cores. See, for example, *Multiparticulate Oral Drug Delivery*; Marcel Dekker: 1994; and *Pharmaceutical Pelletization Technology*; Marcel Dekker: 1989.

**[00183]** In some embodiments, other excipients as described herein are blended with the pharmaceutical compositions to aid in processing and forming the multiparticulates. The resulting particles may themselves constitute the multiparticulate device or may be coated by various film-forming materials, such as enteric polymers, water-swallowable, and water-soluble polymers. The multiparticulates can be further processed as a capsule or a tablet.

#### 4. Targeted Delivery

**[00184]** In some embodiments, the pharmaceutical compositions provided herein are formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated, including liposome-, resealed erythrocyte-, and antibody-based delivery systems. Examples include, but are not limited to, U.S. Pat. Nos. 6,316,652; 6,274,552; 6,271,359; 6,253,872; 6,139,865; 6,131,570; 6,120,751; 6,071,495; 6,060,082; 6,048,736; 6,039,975; 6,004,534; 5,985,307; 5,972,366; 5,900,252; 5,840,674; 5,759,542; and 5,709,874.

#### Methods of Use

##### **Cancer**

**[00185]** In some embodiments, disclosed herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (IIa), or a pharmaceutically acceptable salt, solvate, or

stereoisomer thereof. In some embodiments, disclosed herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

**[00186]** In some embodiments, the disclosed methods are useful in the prevention and treatment of solid tumors, soft tissue tumors, and metastases thereof. Exemplary solid tumors include malignancies (e.g., sarcomas, adenocarcinomas, and carcinomas) of the various organ systems, such as those of lung, breast, lymphoid, gastrointestinal (e.g., colon), and genitourinary (e.g., renal, urothelial, or testicular tumors) tracts, pharynx, prostate, and ovary. Exemplary adenocarcinomas include colorectal cancers, renal-cell carcinoma, liver cancer, non-small cell carcinoma of the lung, and cancer of the small intestine.

**[00187]** In some embodiments, the disclosed methods are useful in the prevention and treatment of LKB1 deficient tumors. In some embodiments, the cancer with LKB1 deficient tumor is a gastrointestinal cancer. In some embodiments, the gastrointestinal cancer is colorectal cancer, small intestinal cancer, gastric cancer, or pancreatic cancer. In some embodiments, the cancer with LKB1 deficient tumor is a gynecological cancer. In some embodiments, the gynecological cancer is breast cancer, ovarian cancer, SCTAT, cervical cancer, prostate cancer, or testicular cancer. In some embodiments, the cancer with LKB1 deficient tumor is a lung cancer. In some embodiments, the lung cancer is non-small cell lung cancer-adenocarcinoma, non-small cell lung cancer-squamous cell, large cell lung cancer, or non-small cell lung cancer. In some embodiments, the cancer with LKB1 deficient tumor is melanoma. In some

embodiments, the cancer with LKB1 deficient tumor is soft tissue cancer. In some embodiments, the cancer with LKB1 deficient tumor is renal cancer. In some embodiments, the cancer with LKB1 deficient tumor is brain cancer.

**[00188]** In some embodiments, the disclosed methods are also useful in treating non-solid cancers.

**[00189]** In some embodiments, the disclosed methods are also useful in treating cancers include, but are not limited to: Adrenocortical Carcinoma, AIDS-Related Cancers (Kaposi Sarcoma, AIDS-Related Lymphoma, Primary CNS Lymphoma), Anal Cancer, Appendix Cancer, Astrocytomas, Atypical Teratoid/Rhabdoid Tumor, Central Nervous System, Basal Cell Carcinoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer Ewing Sarcoma Family of Tumors, Osteosarcoma and Malignant Fibrous Histiocytoma, Brain Stem Glioma, Brain Tumor (Astrocytomas, Central Nervous System Atypical Teratoid/Rhabdoid Tumor, Central Nervous System Embryonal Tumors, Central Nervous System Germ Cell Tumors, Craniopharyngioma, Ependymoma), Breast Cancer, Bronchial Tumors, Carcinoid Tumor, Gastrointestinal, Carcinoma of Unknown Primary, Cardiac (Heart) Tumors, Atypical Teratoid/Rhabdoid Tumor, Embryonal Tumors, Germ Cell Tumor, Cervical Cancer, Cholangiocarcinoma, Chordoma, Chronic Myeloproliferative Neoplasms, Colon Cancer, Colorectal Cancer, Craniopharyngioma, Cutaneous T-Cell Lymphoma, Ductal Carcinoma In Situ (DCIS), Embryonal Tumors, Endometrial Cancer, Ependymoma, Esophageal Cancer, Esthesioneuroblastoma, Ewing Sarcoma, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Eye Cancer, Intraocular Melanoma, Retinoblastoma, Fallopian Tube Cancer, Fibrous Histiocytoma of Bone, Malignant, and Osteosarcoma, Gallbladder Cancer, Gastric (Stomach) Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Stromal Tumors (GIST), Germ Cell Tumor, Ovarian Cancer, Testicular Cancer, Gestational Trophoblastic Disease, Head and Neck Cancer, Heart Cancer, Hepatocellular (Liver) Cancer, Histiocytosis, Langerhans Cell, Hypopharyngeal Cancer, Intraocular Melanoma, Islet Cell Tumors, Pancreatic Neuroendocrine Tumors, Kidney, Renal Cell, Langerhans Cell Histiocytosis, Laryngeal Cancer, Leukemia (Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), Chronic Lymphocytic Leukemia (CLL), Chronic Myelogenous Leukemia (CML), Hairy Cell Leukemia), Lip and Oral Cavity Cancer, Liver Cancer (Primary), Lung Cancer (small cell lung cancer, non-small cell lung cancer), Lymphoma (Burkitt Lymphoma, Hodgkin Lymphoma, Non-Hodgkin Lymphoma, Macroglobulinemia, Waldenström), Male Breast Cancer, Malignant Fibrous Histiocytoma of Bone and Osteosarcoma, Melanoma, Intraocular (Eye), Merkel Cell Carcinoma, Mesothelioma, Malignant, Metastatic Squamous Neck Cancer with Occult Primary, Midline Tract Carcinoma

Involving NUT Gene, Mouth Cancer, Multiple Endocrine Neoplasia Syndromes, Multiple Myeloma/Plasma Cell Neoplasm, Mycosis Fungoides, Myelodysplastic Syndromes, Myelodysplastic/Myeloproliferative Neoplasms, Myeloma, Multiple Myeloma, Myeloproliferative Neoplasms, Chronic, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Oral Cancer, Lip and Oral Cavity Cancer, Oropharyngeal Cancer, Osteosarcoma and Malignant Fibrous Histiocytoma of Bone, Ovarian Cancer, Epithelial, Germ Cell Tumor, Low Malignant Potential Tumor, Pancreatic Cancer, Pancreatic Neuroendocrine Tumors (Islet Cell Tumors), Papillomatosis, Paraganglioma, Paranasal Sinus and Nasal Cavity Cancer, Parathyroid Cancer, Penile Cancer, Pharyngeal Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Pleuropulmonary Blastoma, Primary Peritoneal Cancer, Prostate Cancer, Rectal Cancer, Renal Cell (Kidney) Cancer, Renal Pelvis and Ureter, Transitional Cell Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoma, Osteosarcoma (Bone Cancer), Rhabdomyosarcoma, Soft Tissue, Uterine, Sézary Syndrome, Skin Cancer, Melanoma, Merkel Cell Carcinoma, Non-melanoma Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Cell Carcinoma, Squamous Neck Cancer with Occult Primary, Stomach (Gastric) Cancer, Testicular Cancer, Throat Cancer, Thymoma and Thymic Carcinoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Ureter and Renal Pelvis, Transitional Cell Cancer, Urethral Cancer, Uterine Cancer, Endometrial cancer, Uterine Sarcoma, Vaginal Cancer, Vulvar Cancer, Wilms Tumor. Metastases of the aforementioned cancers can also be treated or prevented in accordance with the methods described herein.

**[00190]** In some embodiments, the cancer is an IDH1 mutant cancer. In some embodiments, the IDH1 mutant cancer is a glioma, for example, a low grade glioma. In some embodiments, the IDH1 mutant cancer is a sarcoma, for example, chondrosarcoma. In some embodiments, the IDH1 mutant cancer is a carcinoma, for example, intrahepatic cholangiocarcinoma. In some embodiments, the IDH1 mutant cancer is a leukemia, for example, Acute Myeloid Leukemia (AML). In some embodiments, the IDH1 mutant cancer is a neoplasm, for example Myelodysplastic/ Myeloproliferative Neoplasms (MDS/MPN). In some embodiments, the IDH1 mutant cancer is associated with Maffucci syndrome. In some embodiments, the IDH1 mutant cancer is associated with Ollier disease. In some embodiments, the IDH1 mutant cancer is colon cancer, melanoma, lung cancer, or prostate cancer.

#### Combination Therapies

**[00191]** In some embodiments, a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer

thereof, is administered together with an additional cancer treatment. In some embodiments, disclosed herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and an additional cancer treatment. Exemplary cancer treatments include, for example, chemotherapy, targeted therapies such as antibody therapies, immunotherapy, and hormonal therapy. Examples of each of these treatments are provided below.

### 1. Chemotherapy

**[00192]** In some embodiments, a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered with chemotherapy. In some embodiments, disclosed herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and an additional cancer treatment, wherein the additional cancer treatment is chemotherapy. Chemotherapy is the treatment of cancer with drugs that can destroy cancer cells. “Chemotherapy” usually refers to cytotoxic drugs which affect rapidly dividing cells in general, in contrast with targeted therapy. Chemotherapy drugs interfere with cell division in various possible ways, e.g., with the duplication of DNA or the separation of newly formed chromosomes. Most forms of chemotherapy target all rapidly dividing cells and are not specific for cancer cells, although some degree of specificity may come from the inability of many cancer cells to repair DNA damage, while normal cells generally can.

**[00193]** Examples of chemotherapeutic agents used in cancer therapy include, for example, antimetabolites (e.g., folic acid, purine, and pyrimidine derivatives) and alkylating agents (e.g., nitrogen mustards, nitrosoureas, platinum, alkyl sulfonates, hydrazines, triazines, aziridines, spindle poison, cytotoxic agents, topoisomerase inhibitors and others). Exemplary agents include Aclarubicin, Actinomycin, Alitretinon, Altretamine, Aminopterin, Aminolevulinic acid, Amrubicin, Amsacrine, Anagrelide, Arsenic trioxide, Asparaginase, Atrasentan, Belotecan, Bexarotene, endamustine, Bleomycin, Bortezomib, Busulfan, Camptothecin, Capecitabine, Carboplatin, Carboquone, Carmofur, Carmustine, Celecoxib, Chlorambucil, Chlormethine, Cisplatin, Cladribine, Clofarabine, Crisantaspase, Cyclophosphamide, Cytarabine, Dacarbazine, Dactinomycin, Daunorubicin, Decitabine, Demecolcine, Docetaxel, Doxorubicin, Efavoxir, Efavoxir, Elesclomol, Elsamitrucin, Enocitabine, Epirubicin, Estramustine, Etoposide, Etoposide, Floxuridine, Fludarabine, Fluorouracil (5FU), Fotemustine, Gemcitabine, Gliadel implants,



Hydroxycarbamide, Hydroxyurea, Ibrutinib, Idarubicin, Ifosfamide, Irinotecan, Irofulven, Ixabepilone, Larotaxel, Leucovorin, Liposomal doxorubicin, Liposomal daunorubicin, Lonidamine, Lomustine, Lucanthone, Mannosulfan, Masoprocil, Melphalan, Mercaptopurine, Mesna, Methotrexate, Methyl aminolevulinate, Mitobronitol, Mitoguazone, Mitotane, Mitomycin, Mitoxantrone, Nedaplatin, Nimustine, Oblimersen, Omacetaxine, Ortataxel, Oxaliplatin, Paclitaxel, Pegaspargase, Pemetrexed, Pentostatin, Pirarubicin, Pixantrone, Plicamycin, Porfimer sodium, Prednimustine, Procarbazine, Raltitrexed, Ranimustine, Rubitecan, Sapacitabine, Semustine, Sitimagene ceradenovec, Strataplatin, Streptozocin, Talaporfin, Tegafur-uracil, Temoporfin, Temozolomide, Teniposide, Tesetaxel, Testolactone, Tetranitrate, Thiotepa, Tiazofurine, Tioguanine, Tipifarnib, Topotecan, Trabectedin, Triaziquone, Triethylenemelamine, Triplatin, Tretinoin, Treosulfan, Trofosfamide, Uramustine, Valrubicin, Verteporfin, Vinblastine, Vincristine, Vindesine, Vinflunine, Vinorelbine, Vorinostat, Zorubicin, and other cytostatic or cytotoxic agents described herein. Because some drugs work better together than alone, two or more drugs are often given at the same time. Often, two or more chemotherapy agents are used as combination chemotherapy.

## 2. Targeted Therapy

**[00194]** In some embodiments, a compound of (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered with a targeted therapy. In some embodiments, disclosed herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and an additional cancer treatment, wherein the additional cancer treatment is a targeted therapy. Targeted therapy constitutes the use of agents specific for the deregulated proteins of cancer cells. Small molecule targeted therapy drugs are generally inhibitors of enzymatic domains on mutated, overexpressed, or otherwise critical proteins within the cancer cell. Prominent examples are the tyrosine kinase inhibitors such as axitinib, bosutinib, cediranib, dasatinib, erlotinib, imatinib, gefitinib, lapatinib, lestaurtinib, nilotinib, semaxanib, sorafenib, sunitinib, and vandetanib, and also cyclin-dependent kinase inhibitors such as alvocidib and seliciclib. In some embodiments, the targeted therapy is a mutant BRAF inhibitor, such as vemurafenib or dabrafenib. In some embodiments, the targeted therapy (second therapeutic agent) is a BRAF inhibitor selected from dabrafenib, vemurafenib, encorafenib, TAK-580, LY3009120, BGB-283, HM955573, and PLX8394. In some embodiments, the targeted therapy (second therapeutic agent) is an mTOR inhibitor. In

some embodiments, the second therapeutic agent is an mTOR inhibitor selected from everolimus, TAK-228, AZD2014, LY3023414, and gedatolisib.

**[00195]** In some embodiments, the targeted therapy is a MEK inhibitor, such as trametinib, cobimetinib, binimetinib, selumetinib. In some embodiments, the targeted therapy is a combination of a mutant BRAF inhibitor and a MEK inhibitor, such as a combination of dabrafenib/trametinib or vemurafenib/cobimetinib. In some embodiments, the targeted therapy is a combination of a mutant BRAF inhibitor and a MEK inhibitor, wherein the BRAF inhibitor is selected from dabrafenib, vemurafenib, encorafenib, TAK-580, LY3009120, BGB-283, HM955573, and PLX8394. In some embodiments, the targeted therapy is an IDH1 inhibitor (for example, AGI-5198, AG-120 and AG-881), a Non-Small Cell Lung Cancer SOC agents, an androgen receptor antagonist (for example, bicalutamide, flutamide, nitulamide, apalutamide, enzalutamide, abiraterone acetate, ODM-201, or 4-((1R,2R)-2-Hydroxycyclohexyl)-2(trifluoromethyl)benzotrile (PF 998425)), or an estrogen receptor antagonist (for example,  $7\alpha,17\beta$ -[9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl]estra-1,3,5(10)-triene-3,17-diol (ICI 182,780), 1,3-Bis(4-hydroxyphenyl)-4-methyl-5-[4-(2-piperidinyloxy)phenol]-1H-pyrazole dihydrochloride (MPP dihydrochloride), 4-[2-phenyl-5,7-bis(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-3-yl]phenol (PHTPP), 3-[4-(2,4-Bis-trifluoromethylbenzyloxy)-3-methoxyphenyl]-2-cyano-N-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)acrylamide (XCT 790), or 2-(4-hydroxyphenyl)-3-methyl-1-[10-(pentylsulfonyl)decyl]-1H-indol-5-ol (ZK 164015)). Monoclonal antibody therapy is another strategy in which the therapeutic agent is an antibody which specifically binds to a protein on the surface of the cancer cells. Examples include the anti-HER2/neu antibody trastuzumab typically used in breast cancer, and the anti-CD20 antibody rituximab and tositumomab typically used in a variety of B-cell malignancies. Other exemplary antibodies include cetuximab, panitumumab, trastuzumab, alemtuzumab, bevacizumab, edrecolomab, and gemtuzumab. Exemplary fusion proteins include aflibercept and denileukin diftitox.

**[00196]** Targeted therapy can also involve small peptides as “homing devices” which can bind to cell surface receptors or affected extracellular matrix surrounding the tumor. Radionuclides which are attached to these peptides (e.g., RGDs) eventually kill the cancer cell if the nuclide decays in the vicinity of the cell.

### 3. Immunotherapy

**[00197]** In some embodiments, a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered with an immunotherapy. In some embodiments, disclosed herein is a

method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and an additional cancer treatment, wherein the additional cancer treatment is immunotherapy. Cancer immunotherapy refers to a diverse set of therapeutic strategies designed to induce the patient's own immune system to fight the tumor. Contemporary methods for generating an immune response against tumors include intravesicular BCG immunotherapy for superficial bladder cancer, and use of interferons and other cytokines to induce an immune response in renal cell carcinoma and melanoma patients. In some embodiments, a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered with an immunotherapy wherein the immunotherapy is selected from antibodies against PD1, PD1L, and CTLA4. In some embodiments, disclosed herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and an additional cancer treatment, wherein the additional cancer treatment is a PD1 antibody. In some embodiments, disclosed herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a PD1 antibody, wherein the cancer is melanoma.

**[00198]** In some embodiments, disclosed herein is a method of modulating granulocytic myeloid-derived suppressor cells (G-MDSCs) in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and an additional cancer treatment, wherein the additional cancer treatment is immunotherapy. In some embodiments, disclosed herein is a method of modulating granulocytic myeloid-derived suppressor cells (G-MDSCs) in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and an additional cancer treatment, wherein the additional cancer treatment is immunotherapy and the immunotherapy is selected from antibodies against PD1, PD1L, and CTLA4. In some embodiments, disclosed herein is a method of modulating granulocytic myeloid-derived suppressor cells (G-MDSCs) in a subject, comprising administering to a subject

a therapeutically effective amount of a compound Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and an additional cancer treatment, wherein the additional cancer treatment is a PD1 antibody.

**[00199]** Allogeneic hematopoietic stem cell transplantation can be considered a form of immunotherapy, since the donor's immune cells will often attack the tumor in a graft-versus-tumor effect.

#### 4. Hormonal Therapy

**[00200]** In some embodiments, a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered with a hormonal therapy. In some embodiments, disclosed herein is a method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and an additional cancer treatment, wherein the additional cancer treatment is hormonal therapy. In some embodiments, the cancer growth is inhibited by providing or blocking certain hormones. Common examples of hormone-sensitive tumors include certain types of breast and prostate cancers. Removing or blocking estrogen or testosterone is often an important additional treatment. In certain cancers, administration of hormone agonists, such as progestogens may be therapeutically beneficial.

#### 5. Additional combination therapy

**[00201]** In some embodiments, a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered with 2-deoxy glucose, monocarboxylate transporters (for example, MCT1 or MCT4), or glucose transporters (for example GLUT4).

#### **Diabetes**

**[00202]** In some embodiments, disclosed herein is a method of treating diabetes in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating diabetes in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating diabetes in a subject, comprising administering to a subject a therapeutically effective amount of a

compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating diabetes in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating diabetes in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating diabetes in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating diabetes in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating diabetes in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating diabetes in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating diabetes in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating diabetes in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating diabetes in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

**[00203]** Methods disclose herein are used for the treatment and/or prevention of diabetes, including, for example, type 1 and type 2 diabetes, and related diseases. In some embodiments, the methods are used for treating prediabetes, and/or glucose intolerance. In some embodiments the methods help with glycemic control, as monitored by, for example, average glucose and/or glycosylated hemoglobin levels. Further, in some embodiments, the patient being treated may suffer from insulin resistance. In other aspects, the present invention provides for treatments and uses in the prevention of diabetes onset in patients afflicted with, for example, insulin resistance,

prediabetes, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and acanthosis nigricans.

#### Combination Therapies

**[00204]** In some embodiments, a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered together with an additional diabetes treatment. Exemplary diabetes treatments include:

**[00205]** Insulin and insulin derivatives are selected from insulin glargine, insulin glulisine, insulin detemir, insulin lispro, insulin degludec, insulin aspart, basal insulin and analogues (e.g. LY2605541, LY2963016, NN1436), PEGylated insulin lispro (e.g. LY-275585), long-acting insulins, intermediate-acting insulins, and fast-acting and short-acting insulins. Also suitable are those insulin derivatives which are bonded to albumin or another protein by a bifunctional linker.

**[00206]** Glucagon-like-peptide 1 (GLP-1), GLP-1 analogues, and GLP-1 receptor agonists, for example: lixisenatide, exenatide, liraglutide, semaglutide, taspeglutide, albiglutide, dulaglutide, ACP-003, CJC-1 134-PC, GSK-2374697, PB-1023, TTP-054, langlenatide (HM-1 1260C), CM-3, GLP-1 Eligen, AB-201, ORMD-0901, NN9924, NN9926, NN9927, Nodexen, Viador-GLP-1, CVX-096, ZYOG-1, ZYD-1, ZP-3022, CAM- 2036, DA-3091, DA-15864, ARI-2651, ARI-2255, exenatide-XTEN (VRS-859), exenatide-XTEN + Glucagon-XTEN (VRS-859 + AMX-808) and polymer-bound GLP-1 and GLP-1 analogues. Dual GLP-1/GIP agonists (e.g. RG-7697 (MAR-701), MAR-709, BHM081, BHM089, BHM098). Dual GLP-1/glucagon receptor agonists (e.g. BHM-034, OAP-189 (PF-05212389, TKS- 1225), TT-401/402, ZP2929, LAPS-HMOXM25, MOD-6030). Dual GLP-1 /gastrin agonists (e.g. ZP-3022).

**[00207]** Glucagon receptor agonists or antagonists, glucose-dependent insulinotropic polypeptide (GIP) receptor agonists or antagonists, ghrelin antagonists or inverse agonists, xenin and analogues thereof, dipeptidyl peptidase-IV (DPP-4) inhibitors, for example: alogliptin, linagliptin, saxagliptin, sitagliptin, anagliptin, teneligliptin, trelagliptin, vildagliptin, gemigliptin, omarigliptin, evogliptin, dutogliptin, DA-1229, MK-3102, KM-223, KRP-104, PBL-1427, Pinoxacin hydrochloride, and Ari- 2243, sodium-dependent glucose transporter 2 (SGLT-2) inhibitors, for example: canagliflozin, dapagliflozin, remogliflozin, remogliflozin etabonate, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, ertugliflozin, EGT-0001442, LIK-066, SBM-TFC- 039, and KGA-3235 (DSP-3235), dual inhibitors of SGLT-2 and SGLT-1 (e.g. LX-421 1, LIK066), biguanides (e.g. metformin, buformin), thiazolidinediones (e.g. pioglitazone, rosiglitazone), glitazone analogues (e.g. lobeglitazone), peroxisome

proliferator-activated receptors (PPAR-)(alpha, gamma or alpha/gamma) agonists or modulators (e.g. saroglitazar), or PPAR gamma partial agonists (e.g. Int-131).

**[00208]** Sulfonylureas (e.g. tolbutamide, glibenclamide, glimepiride, glipizide) and meglitinides (e.g. nateglinide, repaglinide, mitiglinide), alpha-glucosidase inhibitors (e.g. acarbose, miglitol, voglibose), amylin and amylin analogues (e.g. pramlintide) G-protein coupled receptor 19 (GPR19) agonists (e.g. GSK-1292263, PSN-821, MBX-2982, APD-597, ARRY-981, ZYG-19, DS-8500, HM-47000, YH-Chem1), GPR40 agonists (e.g. TUG-424, P-1736, P-1187, JTT-851, GW9508, CNX-011-67, AM-1638, AM-5262), GPR120 agonists and GPR142 agonists, systemic or low-absorbable TGR5 (GPBAR1 = G-protein-coupled bile acid receptor 1) agonists (e.g. INT-777, XL-475, SB756050).

**[00209]** Diabetes immunotherapeutics, for example: oral C-C chemokine receptor type 2 (CCR-2) antagonists (e.g. CCX-140, JNJ-41443532), interleukin 1 beta (IL-1 .beta.) antagonists (e.g. AC-201), or oral monoclonal antibodies (MoA) (e.g. methalozamide, WP808, PAZ-320, P-1736, PF-05175157, PF-04937319).

**[00210]** Anti-inflammatory agents for the treatment of the metabolic syndrome and diabetes, for example: nuclear factor kappa B inhibitors. Adenosine monophosphate-activated protein kinase (AMPK) stimulants, for example: Imeglimin (PXL-008), Debio-0930 (MT-63-78), R-118. Inhibitors of 11-beta-hydroxysteroid dehydrogenase 1 (11-beta-HSD-1) (e.g. LY2523199, BMS770767, RG-4929, BMS816336, AZD-8329, HSD-016, BI-135585).

**[00211]** Activators of glucokinase (e.g. PF-04991532, TTP-399 (GK1-399), GKM-001 (ADV-1002401), ARRY-403 (AMG-151), TAK-329, TMG-123, ZYGK1).

**[00212]** Inhibitors of diacylglycerol O-acyltransferase (DGAT) (e.g. pradigastat (LCQ-908)), inhibitors of protein tyrosine phosphatase 1 (e.g. trodusquemine), inhibitors of glucose-6-phosphatase, inhibitors of fructose-1,6-bisphosphatase, inhibitors of glycogen phosphorylase, inhibitors of phosphoenol pyruvate carboxykinase, inhibitors of glycogen synthase kinase, inhibitors of pyruvate dehydrogenase kinase.

**[00213]** Modulators of glucose transporter-4, somatostatin receptor 3 agonists (e.g. MK-4256).

**[00214]** One or more lipid lowering agents, for example: 3-hydroxy-3-methylglutaryl-coenzym-A-reductase (HMG-CoA-reductase) inhibitors such as simvastatin, atorvastatin, rosuvastatin, pravastatin, fluvastatin, pitavastatin, lovastatin, mevastatin, rivastatin, cerivastatin, fibrates such as bezafibrate, ciprofibrate, fenofibrate, gemfibrozil, etofibrate, simfibrate, ronifibrate, clinofibrate, clofibrate, nicotinic acid and derivatives thereof (e.g. niacin, including slow release formulations of niacin), nicotinic acid receptor 1 agonists (e.g. GSK-256073), PPAR-delta agonists, acetyl-CoA-acetyltransferase (ACAT) inhibitors (e.g. avasimibe),

cholesterol absorption inhibitors (e.g. ezetimibe, S-556971), bile acid-binding substances (e.g. cholestyramine, colesevelam), ileal bile acid transport (IBAT) inhibitors (e.g. GSK-2330672, LUM-002), microsomal triglyceride transfer protein (MTP) inhibitors (e.g. lomitapide (AEGR-733), SLx-4090, granotapide), modulators of proprotein convertase subtilisin/kexin type 9 (PCSK9) (e.g. alirocumab (REGN727/SAR236553), AMG-145, LGT-209, PF-04950615, MPSK3169A, LY3015014, ALD-306, ALN-PCS, BMS-962476, SPC5001, ISIS-394814, 1 B20, LGT-210, 1 D05, BMS-PCSK9Rx-2, SX-PCK9, RG7652), LDL receptor up-regulators, for example liver selective thyroid hormone receptor beta agonists (e.g. eprotirome (KB-21 15), MB0781 1, sobetirome (QRX-431), VIA-3196, ZYT1), HDL-raising compounds such as: cholesteryl ester transfer protein (CETP) inhibitors (e.g. anacetrapib (MK0859), dalcetrapib, evacetrapib, JTT-302, DRL-17822, TA-8995, R-1658, LY-2484595, DS-1442), or dual CETP/PCSK9 inhibitors (e.g. K-312), ATP-binding cassette (ABC1) regulators, lipid metabolism modulators (e.g. BMS-823778, TAP-301, DRL-21994, DRL-21995), phospholipase A2 (PLA2) inhibitors (e.g. darapladib, varespladib, rilapladib), ApoA-I enhancers (e.g. RVX-208, CER-001, MDCO-216, CSL-1 12), cholesterol synthesis inhibitors (e.g. ETC-1002), lipid metabolism modulators (e.g. BMS-823778, TAP-301, DRL-21994, DRL-21995) and omega-3 fatty acids and derivatives thereof (e.g. icosapent ethyl (AMR101), AKR-063, NKPL-66, PRC-4016, CAT-2003).

**[00215]** Treatment of obesity, such as Bromocriptine, phentermine and phentermine formulations or combinations (e.g. Adipex-P, lonamin), benzphetamine, diethylpropion, phendimetrazin, bupropion and combinations, sibutramine, topiramate, zonisamide, tesofensine, opioid antagonists such as naltrexone, cannabinoid receptor 1 (CB1) antagonists (e.g. TM-38837), melanin-concentrating hormone (MCH-1) antagonists (e.g. BMS-830216, ALB-127158(a)), MC4 receptor agonists and partial agonists (e.g. AZD-2820, RM-493), neuropeptide Y5 (NPY5) or NPY2 antagonists (e.g. velneparit, S-234462), NPY4 agonists (e.g. PP-1420), beta-3-adrenergic receptor agonists, leptin or leptin mimetics, agonists of the 5-hydroxytryptamine 2c (5HT2c) receptor (e.g. lorcaserin), pramlintide/metreleptin, lipase inhibitors such as cetilistat, orlistat, angiogenesis inhibitors (e.g. ALS-L1023), betahistidine and histamine H3 antagonists (e.g. HPP-404), AgRP (agouti related protein) inhibitors (e.g. TTP-435), serotonin re-uptake inhibitors such as fluoxetine, duloxetine, dual or triple monoamine uptake inhibitors (dopamine, norepinephrine and serotonin re-uptake) such as sertraline, tesofensine, methionine aminopeptidase 2 (MetAP2) inhibitors (e.g. beloranib), and antisense oligonucleotides against production of fibroblast growth factor receptor 4 (FGFR4) (e.g. ISIS-FGFR4Rx) or prohibitin targeting peptide-1.



**[00216]** Drugs for influencing high blood pressure, chronic heart failure or atherosclerosis, for example: nitric oxide donors, AT1 antagonists or angiotensin II (AT2) receptor antagonists such as telmisartan, candesartan, valsartan, losartan, eprosartan, irbesartan, olmesartan, tasosartan, azilsartan, dual angiotensin receptor blockers (dual ARBs), angiotensin converting enzyme (ACE) inhibitors, ACE-2 activators, renin inhibitors, prorenin inhibitors, endothelin converting enzyme (ECE) inhibitors, endothelin receptor (ET1/ETA) blockers, endothelin antagonists, diuretics, aldosterone antagonists, aldosterone synthase inhibitors, alpha- blockers, antagonists of the alpha-2 adrenergic receptor, beta-blockers, mixed alpha-/beta-blockers, calcium antagonists, calcium channel blockers (CCBs), nasal formulations of the calcium channel blocker diltiazem (e.g. CP-404), dual mineralocorticoid/CCBs, centrally acting antihypertensives, inhibitors of neutral endopeptidase, aminopeptidase-A inhibitors, vaso peptide inhibitors, dual vaso peptide inhibitors such as neprilysin-ACE inhibitors or neprilysin-ECE inhibitors, dual-acting AT receptor-neprilysin inhibitors, dual AT1/ETA antagonists, advanced glycation end- product (AGE) breakers, recombinant renalase, blood pressure vaccines such as anti- RAAS (renin-angiotensin-aldosteron-system) vaccines, AT1- or AT2-vaccines, drugs based on hypertension pharmacogenomics such as modulators of genetic.

Additional combination therapy

**[00217]** In some embodiments, a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered with 2-deoxy glucose, monocarboxylate transporters (for example, MCT1 or MCT4), or glucose transporters (for example GLUT4).

#### **Polycystic ovarian syndrome (PCOS)**

**[00218]** In some embodiments, disclosed herein is a method of treating polycystic ovarian syndrome (PCOS) in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating polycystic ovarian syndrome (PCOS) in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating polycystic ovarian syndrome (PCOS) in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating polycystic ovarian syndrome (PCOS) in a

subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating polycystic ovarian syndrome (PCOS) in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating polycystic ovarian syndrome (PCOS) in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating polycystic ovarian syndrome (PCOS) in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating polycystic ovarian syndrome (PCOS) in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating polycystic ovarian syndrome (PCOS) in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating polycystic ovarian syndrome (PCOS) in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating polycystic ovarian syndrome (PCOS) in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, disclosed herein is a method of treating polycystic ovarian syndrome (PCOS) in a subject, comprising administering to a subject a therapeutically effective amount of a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

#### Combination Therapies

**[00219]** In some embodiments, a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered together with an additional polycystic ovarian syndrome (PCOS) treatment. Exemplary treatments include: metformin and oral contraceptive.

## Combination Therapies with CYP inhibitor

**[00220]** In some embodiments, provided herein is a method of increasing the bioavailability of a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV) in a subject comprising administering to a subject a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments is a method of increasing the bioavailability of a compound of Formula (I) in a subject comprising administering to a subject a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments is a method of increasing the bioavailability of a compound of Formula (Ia) in a subject comprising administering to a subject a compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments is a method of increasing the bioavailability of a compound of Formula (Ib) in a subject comprising administering to a subject a compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments is a method of increasing the bioavailability of a compound of Formula (II) in a subject comprising administering to a subject a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments is a method of increasing the bioavailability of a compound of Formula (IIa) in a subject comprising administering to a subject a compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments is a method of increasing the bioavailability of a compound of Formula (IIb) in a subject comprising administering to a subject a compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments is a method of increasing the bioavailability of a compound of Formula (IIc) in a subject comprising administering to a subject a compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments is a method of increasing the bioavailability of a compound of Formula (III) in a subject comprising administering to a subject a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments is a method of increasing the bioavailability of a compound of Formula (IIIa) in a subject comprising administering to a subject a compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments is a method of increasing the bioavailability of a compound of Formula (IIIb) in a subject comprising administering to a subject a compound of Formula (IIIb), or a

pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments is a method of increasing the bioavailability of a compound of Formula (IV) in a subject comprising administering to a subject a compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor.

**[00221]** In some embodiments, provided herein is a method of decreasing the metabolism of a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV) in a subject comprising administering to a subject compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments, provided herein is a method of decreasing the metabolism of a compound of Formula (I) in a subject comprising administering to a subject compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments, provided herein is a method of decreasing the metabolism of a compound of Formula (Ia) in a subject comprising administering to a subject compound of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments, provided herein is a method of decreasing the metabolism of a compound of Formula (Ib) in a subject comprising administering to a subject compound of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments, provided herein is a method of decreasing the metabolism of a compound of Formula (II) in a subject comprising administering to a subject compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments, provided herein is a method of decreasing the metabolism of a compound of Formula (IIa) in a subject comprising administering to a subject compound of Formula (IIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments, provided herein is a method of decreasing the metabolism of a compound of Formula (IIb) in a subject comprising administering to a subject compound of Formula (IIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments, provided herein is a method of decreasing the metabolism of a compound of Formula (IIc) in a subject comprising administering to a subject compound of Formula (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments, provided herein is a method of decreasing the metabolism of a compound of Formula (III) in a subject comprising administering to a subject compound of

Formula (III), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments, provided herein is a method of decreasing the metabolism of a compound of Formula (IIIa) in a subject comprising administering to a subject compound of Formula (IIIa), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments, provided herein is a method of decreasing the metabolism of a compound of Formula (IIIb) in a subject comprising administering to a subject compound of Formula (IIIb), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor. In some embodiments, provided herein is a method of decreasing the metabolism of a compound of Formula (IV) in a subject comprising administering to a subject compound of Formula (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a cytochrome P450 inhibitor.

**[00222]** In some embodiments, the cytochrome P450 inhibitor is a cytochrome P450 2D6 inhibitor. In some embodiments, the cytochrome P450 2D6 inhibitor is selected from amiodarone, buprenorphine, bupropion, cannabidiol, celecoxib, chlorphenamine, chlorpromazine, cimetidine, cinacalcet, citalopram, clemastine, clomipramine, diphenhydramine, doxepin, doxorubicin, duloxetine, escitalopram, fluoxetine, halofantrine, haloperidol, hydroxyzine, hyperforin, levomepromazine, methadone, metoclopramide, mibefradil, midodrine, moclobemide, paroxetine, perphenazine, promethazine, quinidine, risperidone, ritonavir, sertraline, terbinafine, thioridazine, ticlopidine, tripeleminamine, and zuclopenthixol. In some embodiments, the cytochrome P450 2D6 inhibitor is quinidine.

**[00223]** Depending on the disease to be treated and the subject's condition, a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal or local) routes of administration, and may be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration.

**[00224]** In some embodiments, the dose is in the form of one, two, three, four, five, six, or more sub-doses that are administered at appropriate intervals per day. The dose or sub-doses can be administered in the form of dosage units containing from about 0.1 to about 1000 milligram, from about 0.1 to about 500 milligrams, or from 0.5 about to about 100 milligram active

ingredient(s) per dosage unit, and if the condition of the patient requires, the dose can, by way of alternative, be administered as a continuous infusion.

**[00225]** In certain embodiments, an appropriate dosage level is about 0.01 to about 100 mg per kg patient body weight per day (mg/kg per day), about 0.01 to about 50 mg/kg per day, about 0.01 to about 25 mg/kg per day, or about 0.05 to about 10 mg/kg per day, which is administered in a single or multiple doses. In some embodiments, a suitable dosage level is about 0.01 to about 100 mg/kg per day, about 0.05 to about 50 mg/kg per day, or about 0.1 to about 10 mg/kg per day. In some embodiments, a suitable dosage level within this range is about 0.01 to about 0.1, about 0.1 to about 1.0, about 1.0 to about 10, or about 10 to about 50 mg/kg per day.

### **Kits/Articles of Manufacture**

**[00226]** For use in the therapeutic applications described herein, kits and articles of manufacture are also described herein. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

**[00227]** For example, the container(s) can comprise one or more compounds of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container can be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprise a compound with an identifying description or label or instructions relating to its use in the methods described herein.

**[00228]** A kit will typically comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but are not limited to, buffers, diluents, filters, needles, syringes, carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included.

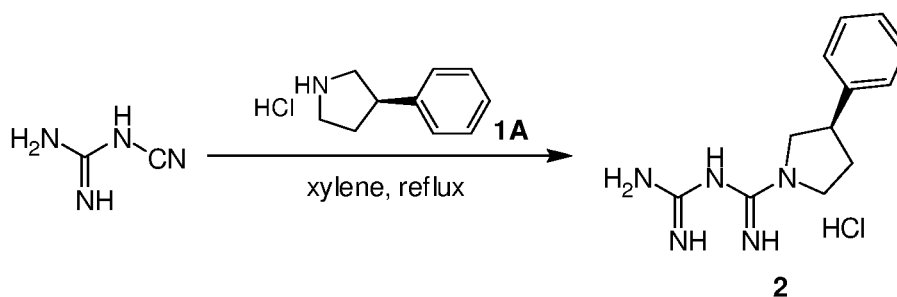
**[00229]** A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate

that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein. These other therapeutic agents may be used, for example, in the amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

### EXAMPLES

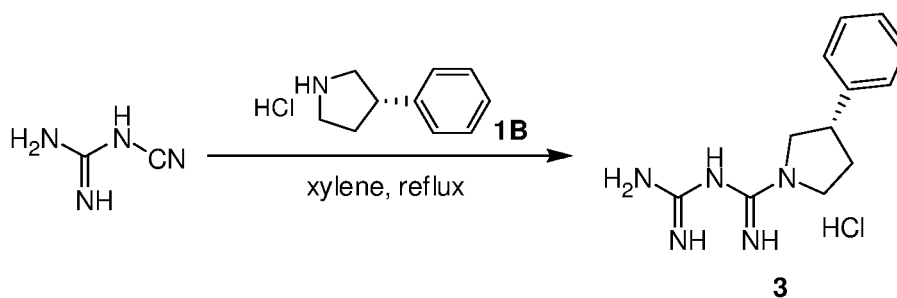
**[00230]** For all of the following examples, standard work-up and purification methods known to those skilled in the art can be utilized. Synthetic methodologies illustrated in Schemes 2, 3, and 4 is intended to exemplify the applicable chemistry through the use of specific examples and are not indicative of the scope of what is claimed herein.

#### **Example 1: Synthesis of (R)-N-carbamimidoyl-3-phenylpyrrolidine-1-carboximidamide hydrochloride (2)**



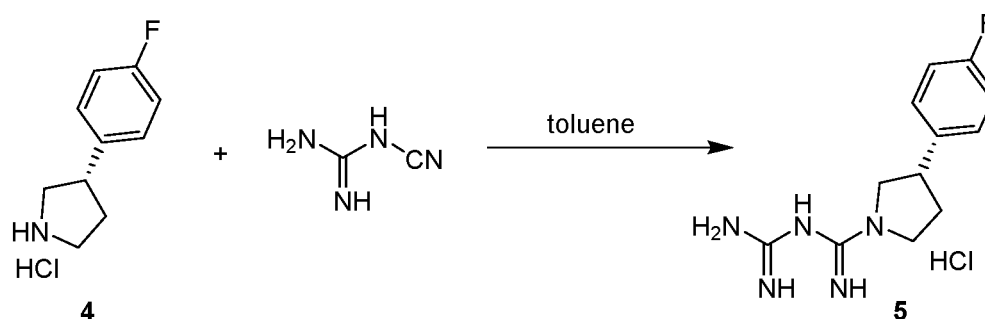
**[00231]** To a solution of 1-cyanoguanidine (300 mg, 3.57 mmol) in xylene (15 mL) was added (3R)-3-phenylpyrrolidine hydrochloride (524 mg, 2.86 mmol). The mixture was stirred at 140 °C for 16 hours. The mixture was cooled and the solids were collected by filtration. The solid was washed with MeCN (2 X 20 mL). The solid was collected and dried under vacuum to give (R)-N-carbamimidoyl-3-phenyl-pyrrolidine-1-carboxamide hydrochloride (510 mg, 66%) as a white solid. LCMS  $m/z$  232.1 ( $M+1$ )<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  7.40-7.27 (m, 4H), 7.27-7.19 (m, 1H), 4.00-3.85 (m, 1H), 3.85-3.60 (m, 1H), 3.60-3.36 (m, 3H), 2.50-2.25 (m, 1H), 2.25-2.05 (m, 1H). <sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>OD)  $\delta$  158.69, 157.48, 140.46, 128.64, 126.87, 53.68, 52.71, 47.88, 46.70, 43.61, 42.90, 32.24.

#### **Example 2: Synthesis of (S)-N-carbamimidoyl-3-phenylpyrrolidine-1-carboximidamide hydrochloride (3)**



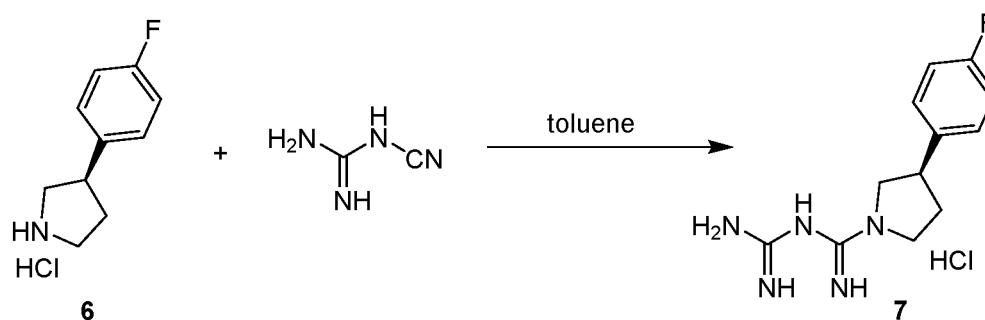
[00232] To a solution of 1-cyanoguanidine (300 mg, 3.57 mmol) in xylene (8 mL) was added (3S)-3-phenylpyrrolidine hydrochloride (525 mg, 2.86 mmol). The mixture was stirred at 140 °C for 16 hours. The mixture was cooled and concentrated. The residue was triturated with 10/1:MeCN/MeOH (20 mL). The resulting solid was collected and dried under vacuum to give (S)-N-carbamimidoyl-3-phenyl-pyrrolidine-1-carboxamide hydrochloride (400 mg, 52%) as a white solid. LCMS  $m/z$  232.1 ( $M+1$ )<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  7.37-7.29 (m, 4H), 7.29-7.22 (m, 1H), 3.98-3.61 (m, 2H), 3.60-3.38 (m, 3H), 2.48-2.29 (m, 1H), 2.23-2.02 (m, 1H). <sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>OD)  $\delta$  158.86, 157.39, 140.56, 128.37, 126.71, 53.50, 52.61, 47.42, 46.99, 43.89, 43.19, 32.34.

**Example 3: Synthesis of (S)-N-carbamimidoyl-3-(4-fluorophenyl)pyrrolidine-1-carboximidamide hydrochloride (5)**



[00233] To a solution of (S)-3-(4-fluorophenyl)pyrrolidine hydrochloride (**4**) (20.00 g, 99.2 mmol) in toluene (800.0 mL) was added 1-cyanoguanidine (10.01 g, 119.0 mmol). The reaction mixture was heated at 110°C for 5h. The reaction mixture was cooled and concentrated. To the residue was added 2-propanol (50 mL). The mixture was stirred at 25°C for 12h and then filtered. The operation was repeated twice to give (S)-N-carbamimidoyl-3-(4-fluorophenyl)pyrrolidine-1-carboximidamide hydrochloride (**5**) (13.40 g, 47.02 mmol, 47%). LCMS  $m/z$  250.0 ( $M+1$ )<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  7.37-7.33 (m, 2H), 7.11-7.07 (m, 2H), 3.93-3.61 (m, 2H), 3.60-3.39 (m, 3H), 2.43-2.30 (m, 1H), 2.23-2.05 (m, 1H).

**Example 4: Synthesis of (R)-N-carbamimidoyl-3-(4-fluorophenyl)pyrrolidine-1-carboximidamide hydrochloride (7)**





[00234] The title compound, (S)-N-carbamimidoyl-3-(4-fluorophenyl)pyrrolidine-1-carboximidamide hydrochloride (**7**) was prepared in a similar manner as outlined in Example 3. (13.40 g, 47.02 mmol, 47%). LCMS  $m/z$  250.4 (M+1)<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  7.37-7.33 (m, 2H), 7.11-7.07 (m, 2H), 3.93-3.61 (m, 2H), 3.60-3.39 (m, 3H), 2.43-2.30 (m, 1H), 2.23-2.05 (m, 1H).

### Example 5: Tumor Cell Growth Inhibition

[00235] Tumor Cell lines

Tumor Cell Line	Tissue Origin	Culture Medium (a)	Cell Plating Medium (b)	Test Cpd Medium (b)	Control	Incubation Time
A549	Lung	DMEM-HG	DMEM-NG	DMEM-NG	Cisplatin	72 h
H460	Lung	DMEM-HG	DMEM-NG	DMEM-NG	Cisplatin	72 h
DU145	Prostate	DMEM-HG	DMEM-NG	DMEM-NG	Cisplatin	72 h
HT1080	Sarcoma	DMEM-HG	DMEM-NG	DMEM-NG	Cisplatin	72 h

(a) All the cells were cultured in DMEM high glucose (HG) media supplemented with 10% FBS at the temperature of 37°C, 5% CO<sub>2</sub> and 95% humidity.

(b) All the cells were cultured in DMEM no glucose (NG) media supplemented with 5 mM glucose, and 10% FBS at the temperature of 37°C, 5% CO<sub>2</sub> and 95% humidity.

[00236] Cell culture

Cells were recovered and maintained in DMEM high glucose (HG) media supplemented with 10% FBS at the temperature of 37°C, 5% CO<sub>2</sub> and 95% humidity.

[00237] Cell Plating

The following procedure was performed:

1. Harvest cells respectively during the logarithmic growth period and counted using Countstar.
2. Spin down the cells, wash and re-suspend them with the new cell plating media (DMEM without glucose in 5 mM glucose).
3. Adjust cell concentrations to optimized density (i.e.  $3.33 \times 10^4$  cells/ml) with respective cell plating medium.
4. Add 90  $\mu$ l cell suspensions to two 96-well plates, plate A (T0 reading) and plate B (compound testing) with the final cell density of 3000 cells/well.
5. Incubate A and B plates for 20 to 24 h before adding the test compounds in humidified incubator at 37°C with 5% CO<sub>2</sub>.

Day 0: T0 reading

6. Add 10  $\mu$ L cell plating medium to each well of plate A group for T0 reading.
7. Add CellTiter-Glo Reagent at equal volume of cell culture medium present in each well (e.g., add 100 $\mu$ l of reagent to 100 $\mu$ l of medium containing cells for a 96-well plate).
8. Mix contents for 2 minutes on an orbital shaker to facilitate cell lysis.
9. Allow the plate to incubate at room temperature for 20 minutes to stabilize luminescent signal.
10. Place Backseal black sticker to the bottom of each plate.
11. Record luminescence (T0) using EnVision Multi Label Reader.

Day 0: Compound treatment

12. For test compounds and Cisplatin, prepare 10 $\times$  serial working solutions with test compound medium.
13. Dispense 10  $\mu$ L (10 $\times$ ) compound solutions in each well (duplicate for each compound concentration) of the plate B.
14. Incubate the test plates for 72 hours in the humidified incubator at 37°C with 5% CO<sub>2</sub>.

Day 3: Plate B group reading

15. Monitor cell growth under a microscope and record cell confluence in vehicle control wells.
16. Add CellTiter-Glo Reagent at equal volume of cell culture medium present in each well (e.g., add 100  $\mu$ L of reagent to 100  $\mu$ L of medium containing cells for a 96 -well plate).
17. Mix contents for 2 minutes on an orbital shaker to induce cell lysis.
18. Allow the plate to incubate at room temperature for 20 minutes to stabilize luminescent signal.
19. Place Backseal black sticker to the bottom of each plate.
20. Record luminescence using EnVision Multi Label Reader.

**[00238]** Data Analysis

Use data are displayed graphically using GraphPad Prism 5.0 curve fitting software.

In order to calculate IC50s, a dose-response curve was fitted using a nonlinear regression model with a sigmoidal dose response. Absolute IC50 were calculated where Y axis set at 50% using XLFit curve fitting software and are shown in Table 1.

Table 1: Tumor Cell Growth Inhibition

Cell Line	Cmpd 2	Cmpd 3	Cmpd 5	Cmpd 7	Phenformin	Metformin
GI50 A549 (uM)	8, 5	30, 7	4	7	33, 70	1,282
GI50 H460 (uM)	15	22	14	23	13	
GI50 DU145 (uM)	13	17, 12	7	14	5	529
GI50 HT1080 (uM)	25	26	22	33	7	

**Example 6: Microsomal Stability Testing****[00239] Materials and Methods**

Test Compounds: Stock Conc.

Compound 2            10 mM

Compound 3            10 mM

Control    10 mM

Control    10 mM

Control    10 mM

**[00240] Buffers**

1. 100 mM potassium phosphate
2. 10 mM MgCl<sub>2</sub>

**[00241] Compound Dilution**

1. Intermediate Solution: Dilute 5 µL of compound or control from stock (10 mM) with 45 µL DMSO, then mixed with 450 µL 1:1Methanol/Water (Conc: 100 µM, 45% MeOH)
2. Working Solution: Dilute 50 µL from intermediate solution (10 mM) with 450 µL 100 nM potassium phosphate buffer (Conc: 10 µM, 4.5% MeOH)

**[00242] NADPH Regenerating System (final isocitric dehydrogenase conc.= 1 unit/mL at incubation)**

1. B-Nicotinamide adenine dinucleotide phosphate
2. Isocitric acid
3. Isocitric dehydrogenase

**[00243] Stop Solution**

Cold CAN including 100 ng/mL tolbutamide and 100 ng/mL labetalol as internal standard.

**[00244] Procedure**

1. Add 10  $\mu$ L compound or control working solution/well to all plates (T0, T5, T10, T20, T30, T60, NCF60) except matrix blank.
2. Dispense 680  $\mu$ L/well microsome solution to 96-well plate as reservoir according to plate map. Then add 80  $\mu$ L/well to every plate by Apricot, incubate the mixture of microsome solution and compound at 37 °C for about 10 min.
3. Add 10  $\mu$ L 100 mM potassium phosphate buffer/well to NCF60, incubate at 37 °C, start timer 1 (Time Point: NCF60 - start time 1:00:00 am, end time 12:00:00 am)
4. After pre-warming, dispense 90  $\mu$ L/well NADPH regenerating system to 96-well plate as reservoir according to plate map. Then add 10  $\mu$ L/well to every plate by Apricot to start reaction.
5. Incubate at 37 °C, start timer 2 (Blank - start time 1:00:00 am, end time 12:00:00 am; T60 - start time 1:00:00 am, end time 12:00:00 am; T30 - start time 12:59:36 am, end time 12:29:36 am; T20 - start time 12:59:12 am, end time 12:39:12 am; T10 - start time 12:58:33 am, end time 12:48:33 am; T5 - start time 12:58:15 am, end time 12:53:15 am; T0 – add stop solution first , then add microsome solution and NADPH regenerating system).
6. Add 300  $\mu$ L/well cold stop solution (4 °C) to terminate the reaction.
7. Shake sampling plates for about 10 min.
8. Centrifuge samples at 4000 rpm for 20 min. under 4 °C.
9. While centrifuging, load 8 x new 96-well plate with 300  $\mu$ L HPLC water, then transfer 100  $\mu$ L of supernatant for HPLC analysis.

#### [00245] Data Analysis

Use equation of first order kinetics to calculate half-life and  $Cl_{int(mic)}$ . Stability data is shown in Table 2.

Table 2: Stability Data

Test	Cmpd 2	Cmpd 3	Cmpd 5	Cmpd 7	Phenformin	Metformin
P450 inhibition (IC <sub>50</sub> , $\mu$ M)	1A2	>50	>50	>50	>50	>50
	2C9	>50	>50	>50	>50	>50
	2C19	>50	>50	>50	>50	>50
	2D6	18	13	>50	>50	47
	3A4 (M)	>50	>50	>50	>50	>50
	3A4 (T)	>50	>50	>50	>50	>50

Microsomal stability (t <sub>1/2</sub> , min) [Ms, H]	>145, >145	>145, >145	>145, >145	>145, >145	53, >145	139, >145
Caco-2 permeability Papp (10 <sup>-6</sup> cm/s) [AB, BA]	0.28, 1.23	0.33, 1.12	0.4, 2.8	0.36, 2.15	0.54, 0.36	0.49, 0.40

**Example 7: Mouse PK**

[00246] Mouse oral PK data is shown in Table 3.

Table 3: Mouse Oral PK Data

	Compound 2	Compound 5	Compound 7	Phenformin
Dose (mg/kg)	100	100	100	100
C <sub>max</sub> (ng/ml)	1,825	1,029	905	1,578
T <sub>max</sub> (h)	0.5	2.13	1.75	0.5
AUC <sub>0-24</sub> (ng•h/ml)	5,204	6,608	6,027	2,756
AUC <sub>0-inf</sub> (ng•h/ml)	5,286	6,771	6,491	2,781
Bioavailability	37%	36%	35%	19%

**Example 8: Tumor Volume Studies****8A: In vivo efficacy of Compound 5 and BRAFi alone or in combination in the treatment of COLO829 xenografts in female Balb/C nude mice**

[00247] Cell Culture: COLO829 tumor cells were maintained in vitro as a monolayer culture in medium supplemented with 10% fetal bovine serum, at 37°C in an atmosphere of 5% CO<sub>2</sub> in air. The tumor cells were routinely sub-cultured twice weekly. The cells growing in an exponential growth phase were harvested and counted for tumor inoculation.

[00248] Animals: Balb/C nude, female, 6-8 weeks, weighing approximately 18-22 g. A total of 52 (including 30% extra) animals were needed for the study and were purchased from Shanghai BK Laboratory Animal Co., LTD. or other certified vendors.

[00249] Tumor Inoculation: Animals were inoculated subcutaneously at the right flank with COLO829 tumor cells ( $5 \times 10^6$ ) in PBS mixed with Matrigel (50:50) for tumor development. Treatments were started when the average tumor volume reaches average  $\sim 100 \text{ mm}^3$  (tumor spread:  $\sim 70\text{-}150 \text{ mm}^3$ ).

**Efficacy Groups and Treatments**

<b>Group</b>	<b>Treatment</b>	<b>n</b>	<b>Dose (mg/kg)</b>	<b>Dosing Volume (ul/g)</b>	<b>Dosing Route</b>	<b>Schedule</b>
1	Vehicle Control	10	-	10+10	PO	bid *3 weeks
2	Compound 5	10	100	10	PO	qd *3 weeks
3	BRAF <sub>i</sub>	10	20	10	PO	bid *3 weeks
4	Compound 5 + BRAF <sub>i</sub>	10	100+20	10+10	PO	(qd+bid) *3 weeks

**[00250]** Assignments to groups: Before commencement of treatment, all animals were weighed and the tumor volumes were measured. Since the tumor volume can affect the effectiveness of any given treatment, mice were assigned into groups using randomized block design based upon their tumor volumes. After grouping, the tumor volume was measured and updated twice per week.

**[00251]** Endpoints: Tumor sizes were measured two times per week in two dimensions using a caliper, and the volume was expressed in mm<sup>3</sup> using the formula:  $V = 0.5 a \times b^2$  where *a* and *b* are the long and short diameters of the tumor, respectively. The tumor sizes were then used for the calculations of both T-C and T/C values. T-C was calculated with T as the median time (in days) required for the treatment group tumors to reach a predetermined size (e.g., 1000 mm<sup>3</sup>), and C as the median time (in days) for the control group tumors to reach the same size. The T/C value (in percent) is an indication of antitumor effectiveness, T and C are the mean volume of the treated and control groups, respectively, on a given day. TGI was calculated for each group using the formula:  $TGI (\%) = [1 - (T_i - T_0) / (V_i - V_0)] \times 100$ ; T<sub>i</sub> was the average tumor volume of a treatment group on a given day, T<sub>0</sub> was the average tumor volume of the treatment group on the first day of treatment, V<sub>i</sub> was the average tumor volume of the vehicle control group on the same day with T<sub>i</sub>, and V<sub>0</sub> was the average tumor volume of the vehicle group on the first day of treatment. Tumor weight was measured at study termination. The T/C value (in percent) was calculated where T and C are the mean tumor weights of the treated and control groups, respectively. Colo829 tumor volume through 21 days of treatment with Compound 5, a BRAF inhibitor, and a Compound 5/BRAF inhibitor combination is shown in Figure 1.

**8B: In vivo efficacy of Compound 5 and mTORi alone or in combination in the treatment of A549 xenografts in female Balb/C nude mice**

[00252] Cell Culture: A549 tumor cells were maintained in vitro as a monolayer culture in medium supplemented with 10% fetal bovine serum, at 37°C in an atmosphere of 5% CO<sub>2</sub> in air. The tumor cells were routinely sub-cultured twice weekly. The cells growing in an exponential growth phase were harvested and counted for tumor inoculation.

[00253] Animals: Balb/C nude, female, 6-8 weeks, weighing approximately 18-22 g. A total of 105 (including 30% extra) animals were needed for the study and were purchased from Shanghai BK Laboratory Animal Co., LTD. or other certified vendors.

[00254] Tumor Inoculation: Animals were inoculated subcutaneously at the right flank with A549 tumor cells ( $5 \times 10^6$ ) in 100  $\mu$ L PBS for tumor development. Treatments were started when the average tumor volume reaches average  $\sim 100 \text{ mm}^3$  (tumor spread:  $\sim 70\text{-}150 \text{ mm}^3$ ).

**Efficacy Groups and Treatments**

Group	Treatment	n	Dose (mg/kg)	Dosing Volume (ul/g)	Dosing Route	Schedule
1	Vehicle Control	10	-	10	PO	qd *4 weeks
2	Compound 5	10	100	10	PO	qd *4 weeks
3	mTORi	10	1	10	PO	qd *4 weeks
4	Compound 5 + mTORi	10	100+1	10+10	PO	qd *4 weeks

[00255] Assignments to groups: Before commencement of treatment, all animals were weighed and the tumor volumes were measured. Since the tumor volume can affect the effectiveness of any given treatment, mice were assigned into groups using randomized block design based upon their tumor volumes. After grouping, body weights were measured and updated daily for the first 5 days of dosing, then regularly scheduled twice weekly thereafter. The tumor volume was measured and updated twice weekly.

[00256] Endpoints: Tumor sizes were measured two times per week in two dimensions using a caliper, and the volume was expressed in  $\text{mm}^3$  using the formula:  $V = 0.5 a \times b^2$  where  $a$  and  $b$  are the long and short diameters of the tumor, respectively. The tumor sizes were then used for

the calculations of both T-C and T/C values. T-C was calculated with T as the median time (in days) required for the treatment group tumors to reach a predetermined size (e.g., 1000 mm<sup>3</sup>), and C as the median time (in days) for the control group tumors to reach the same size. The T/C value (in percent) is an indication of antitumor effectiveness, T and C are the mean volume of the treated and control groups, respectively, on a given day. TGI was calculated for each group using the formula:  $TGI (\%) = [1 - (T_i - T_0) / (V_i - V_0)] \times 100$ ; T<sub>i</sub> was the average tumor volume of a treatment group on a given day, T<sub>0</sub> was the average tumor volume of the treatment group on the first day of treatment, V<sub>i</sub> was the average tumor volume of the vehicle control group on the same day with T<sub>i</sub>, and V<sub>0</sub> was the average tumor volume of the vehicle group on the first day of treatment. Tumor weight was measured at study termination. The T/C value (in percent) was calculated where T and C are the mean tumor weights of the treated and control groups, respectively. A549 tumor volume through 21 days of treatment with Compound 5, an mTOR inhibitor, or a Compound 5/mTOR inhibitor combination is shown in Figure 2.

**Example 9: Evaluation of Clinical Safety of Combining a Compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV) with Anticancer Chemotherapy (Phase 1)**

[00257] Study Type: Interventional

[00258] Study Design: Allocation: Randomized  
 Endpoint Classification: Safety Study  
 Intervention Model: Parallel Assignment  
 Masking: Open Label  
 Primary Purpose: Treatment

[00259] Primary Outcome Measures:

- Incidence of dose limiting toxicity when a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV) is added to chemotherapy [Time Frame: 1 cycle (at least 3 weeks)] [Designated as safety issue: Yes]

[00260] The primary endpoint of the study will be to determine whether a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV) can be safely added to a chemotherapy regimen that is previously well tolerated. The rate of dose limiting toxicities will be compared.

[00261] Secondary Outcome Measures:

[00262] Number of Participants with Adverse Events as a Measure of Safety and Tolerability [ Time Frame: 1 cycle (at least 3 weeks) ] [ Designated as safety issue: Yes ]

Secondary endpoints will include assessment of AEs  $\geq$  grade 3 and Serious Adverse Events (SAEs), assessment of safety beyond the first cycle with a compound of Formula (I), (Ia), (Ib),



(II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV), and an exploration of compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV)-chemotherapy drug interactions.

Arms	Assigned Interventions
Experimental: Compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV)	Drug: Compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV)
No Intervention: No compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV)  No compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV) during primary endpoint assessment period (at least 3 weeks). Patients will subsequently be initiated on a compound of Formula (I), (Ia), (Ib), (II), (IIa), (IIb), (IIc), (III), (IIIa), (IIIb), or (IV).	

**[00263] Eligibility**

Ages Eligible for Study: 18 Years or older  
 Genders Eligible for Study: Both  
 Accepts healthy Volunteers: No

**[00264] Criteria**

Inclusion Criteria:

- Histologically or cytologically documented cancer; diagnosis of hepatocellular carcinoma may be made by characteristic radiographic and/or AFP findings 33;
- Intended treatment with, or currently being treated by anti-cancer chemotherapy in the adjuvant or advanced setting;
- Age 18 to 79;
- Adequate renal function (serum creatinine levels <1.5 mg/dL [males], <1.4 mg/dL [females]). If a subject does not meet these criteria, but does have an estimated creatinine

clearance  $\geq 60$  ml/min using the Cockcroft-Gault calculation, they will be allowed. The Cockcroft-Gault formula is  $CrCl = (140 - \text{age}) \times \text{weight}(\text{kg}) \div (\text{Cr} \times 72)$ , where CrCl = estimated creatinine clearance and Cr is plasma creatinine in mg/dL;

- Adequate hepatic parameters, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels  $\leq 2.5 \times$  upper limit of normal (ULN), total bilirubin  $\leq 1.5 \times$  ULN, and alkaline phosphatase levels  $\leq 2.5 \times$  ULN;
- Must anticipate receiving at least 3 cycles (or treatment periods of at least 3-weeks) of chemotherapy;
- Ability to understand and willingness to sign a written informed consent document.

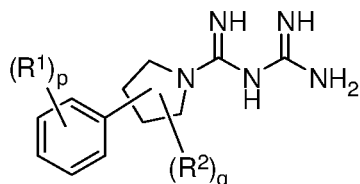
Exclusion Criteria:

- Current use of metformin (within 1 week of start of chemotherapy regimen to be assessed);
- Patients with type 2 diabetes are allowed, however they will be excluded if there is intent to use metformin for treatment of diabetes during the course of the study;
- Undergoing chemotherapy treatment concurrent with radiation therapy;
- Undergoing chemotherapy in a neoadjuvant setting prior to potentially curative surgery;
- Renal disease or renal dysfunction not meeting inclusion criteria;
- Significant medical conditions such as cardiovascular collapse (shock), acute myocardial infarction, septicemia, acute or chronic metabolic acidosis;
- History of, or states associated with, lactic acidosis such as shock or pulmonary insufficiency, alcoholism (acute or chronic), conditions associated with hypoxemia and pancreatitis;
- Severe dehydration;
- Clinical or laboratory evidence of hepatic disease;
- Congestive heart failure requiring pharmacologic treatment, or unstable or acute congestive heart failure;
- Known hypersensitivity to a biguanide compounds;
- Pregnant or lactating women (serum pregnancy test will be performed for all women of child-bearing potential);
- Psychiatric illness or social situation that would limit compliance with study requirements and/or obscure results

## CLAIMS

What is claimed is:

1. A compound of Formula (I) having the structure:



Formula (I);

wherein:

each  $R^1$  is independently halogen, -CN, -NO<sub>2</sub>, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -OC(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -N(R<sup>4</sup>)C(O)R<sup>3</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -N(R<sup>4</sup>)C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, -N(R<sup>4</sup>)S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>;

each  $R^2$  is independently C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each  $R^3$  is independently C<sub>1-6</sub>alkyl;

each  $R^4$  is independently H or C<sub>1-6</sub>alkyl;

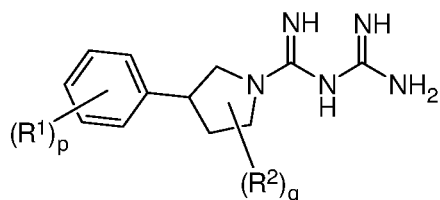
each  $R^5$  and each  $R^6$  are independently H or C<sub>1-6</sub>alkyl; or  $R^5$  and  $R^6$  together with the nitrogen atom to which they are attached form an optionally substituted C<sub>1-6</sub>heterocycloalkyl;

p is 0, 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, having the structure of Formula (Ia):



Formula (Ia).

3. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted

aryl, optionally substituted heteroaryl,  $-C(O)R^3$ ,  $-CO_2R^4$ ,  $-C(O)NR^5R^6$ ,  $-S(O)_2R^3$ , or  $-S(O)_2NR^5R^6$ .

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen,  $-OR^4$ ,  $-NR^4R^4$ ,  $C_{1-6}$ alkyl,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy,  $-CO_2R^4$ , or  $-C(O)NR^5R^6$ .

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen,  $-OR^4$ ,  $C_{1-6}$ alkyl,  $C_{1-6}$ haloalkyl, or  $C_{1-6}$ haloalkoxy.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen,  $-OR^4$ , or  $C_{1-6}$ alkyl.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen.

8. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is  $-OCH_3$ .

9. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $C_{1-6}$ alkyl.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein p is 2.

11. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein p is 1.

12. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein p is 0.

13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkyl or  $C_{1-6}$ alkoxy.

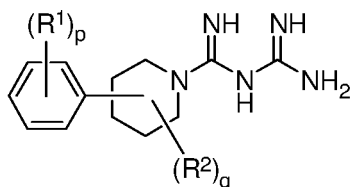
14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkyl.

15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein q is 2.

16. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein q is 1.

17. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein q is 0.

18. A compound of Formula (II) having the structure:



Formula (II);

wherein:

each  $R^1$  is independently halogen, -CN, -NO<sub>2</sub>, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -OC(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -N(R<sup>4</sup>)C(O)R<sup>3</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -N(R<sup>4</sup>)C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, -N(R<sup>4</sup>)S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>;

each  $R^2$  is independently C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each  $R^3$  is independently C<sub>1-6</sub>alkyl;

each  $R^4$  is independently H or C<sub>1-6</sub>alkyl;

each  $R^5$  and each  $R^6$  are independently H or C<sub>1-6</sub>alkyl; or  $R^5$  and  $R^6$  together with the nitrogen atom to which they are attached form an optionally substituted C<sub>1-6</sub>heterocycloalkyl;

$p$  is 1, 2, 3, 4, or 5; and

$q$  is 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

19. The compound of claim 18, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>.

20. The compound of claim 18 or claim 19, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, -CO<sub>2</sub>R<sup>4</sup>, or -C(O)NR<sup>5</sup>R<sup>6</sup>.

21. The compound of any one of claims 18-20, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen, -OR<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, or C<sub>1-6</sub>haloalkoxy.

22. The compound of any one of claims 18-21, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen, -OR<sup>4</sup>, or C<sub>1-6</sub>alkyl.

23. The compound of any one of claims 18-22, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently halogen.

24. The compound of any one of claims 18-22, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is -OCH<sub>3</sub>.

25. The compound of any one of claims 18-22, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently C<sub>1-6</sub>alkyl.

26. The compound of any one of claims 18-25, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein p is 1.

27. The compound of any one of claims 18-25, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein p is 2.

28. The compound of any one of claims 18-25, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein p is 3.

29. The compound of any one of claims 18-28, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy.

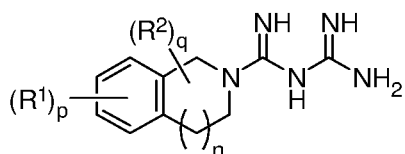
30. The compound of any one of claims 18-29, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl.

31. The compound of any one of claims 18-30, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein q is 2.

32. The compound of any one of claims 18-30, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein q is 1.

33. The compound of any one of claims 18-28, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein q is 0.

34. A compound of Formula (III) having the structure:



Formula (III);

wherein:

each R<sup>1</sup> is independently halogen, -CN, -NO<sub>2</sub>, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -OC(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -N(R<sup>4</sup>)C(O)R<sup>3</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -N(R<sup>4</sup>)C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, -N(R<sup>4</sup>)S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>;

each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R<sup>3</sup> is independently C<sub>1-6</sub>alkyl;

each R<sup>4</sup> is independently H or C<sub>1-6</sub>alkyl;

each R<sup>5</sup> and each R<sup>6</sup> are independently H or C<sub>1-6</sub>alkyl; or R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form an optionally substituted C<sub>1-6</sub>heterocycloalkyl;

n is 0 or 1;

p is 1, 2, 3, or 4; and

q is 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

35. The compound of claim 34, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, optionally substituted C<sub>1-6</sub>heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(O)R<sup>3</sup>, -CO<sub>2</sub>R<sup>4</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>R<sup>3</sup>, or -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>.

36. The compound of claim 34 or claim 35, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, -NR<sup>4</sup>R<sup>4</sup>, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, C<sub>1-6</sub>haloalkoxy, -CO<sub>2</sub>R<sup>4</sup>, or -C(O)NR<sup>5</sup>R<sup>6</sup>.

37. The compound of any one of claims 34-36, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>haloalkyl, or C<sub>1-6</sub>haloalkoxy.

38. The compound of any one of claims 34-37, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen or C<sub>1-6</sub>alkyl.

39. The compound of any one of claims 34-38, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently halogen.

40. The compound of any one of claims 34-38, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>1</sup> is independently C<sub>1-6</sub>alkyl.

41. The compound of any one of claims 34-40, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein p is 1.

42. The compound of any one of claims 34-40, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein p is 2.

43. The compound of any one of claims 34-40, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein p is 3.

44. The compound of any one of claims 34-43, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy.

45. The compound of any one of claims 34-44, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each R<sup>2</sup> is independently C<sub>1-6</sub>alkyl.

46. The compound of any one of claims 34-45, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein q is 2.

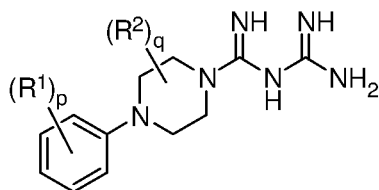
47. The compound of any one of claims 34-45, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein q is 1.

48. The compound of any one of claims 34-43, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein q is 0.

49. The compound of any one of claims 34-48, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein n is 0.

50. The compound of any one of claims 34-48, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein n is 1.

51. A compound of Formula (IV) having the structure:



Formula (IV);

wherein:

each  $R^1$  is independently -CN,  $-NR^4R^4$ ,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy, optionally substituted  $C_{1-6}$ heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl,  $-C(O)R^3$ ,  $-OC(O)R^3$ ,  $-CO_2R^4$ ,  $-N(R^4)C(O)R^3$ ,  $-C(O)NR^5R^6$ ,  $-N(R^4)C(O)NR^5R^6$ ,  $-S(O)_2R^3$ ,  $-N(R^4)S(O)_2R^3$ , or  $-S(O)_2NR^5R^6$ ;

each  $R^2$  is independently  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy, optionally substituted  $C_{1-6}$ heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each  $R^3$  is independently  $C_{1-6}$ alkyl;

each  $R^4$  is independently H or  $C_{1-6}$ alkyl;

each  $R^5$  and each  $R^6$  are independently H or  $C_{1-6}$ alkyl; or  $R^5$  and  $R^6$  together with the nitrogen atom to which they are attached form an optionally substituted  $C_{1-6}$ heterocycloalkyl;

p is 1, 2, 3, 4, or 5; and

q is 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

52. The compound of claim 51, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $-NR^4R^4$ ,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy, optionally substituted  $C_{1-6}$ heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl,  $-C(O)R^3$ ,  $-CO_2R^4$ ,  $-C(O)NR^5R^6$ ,  $-S(O)_2R^3$ , or  $-S(O)_2NR^5R^6$ .



53. The compound of claim 51 or claim 52, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $-NR^4R^4$ ,  $C_{1-6}$ haloalkyl,  $C_{1-6}$ haloalkoxy,  $-CO_2R^4$ , or  $-C(O)NR^5R^6$ .

54. The compound of any one of claims 51-53, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^1$  is independently  $C_{1-6}$ haloalkyl or  $C_{1-6}$ haloalkoxy.

55. The compound of any one of claims 51-54, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein p is 1.

56. The compound of any one of claims 51-54, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein p is 2.

57. The compound of any one of claims 51-54, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein p is 3.

58. The compound of any one of claims 51-57, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkyl or  $C_{1-6}$ alkoxy.

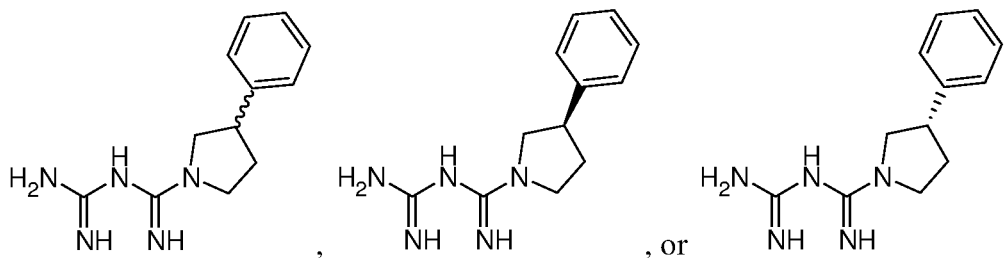
59. The compound of any one of claims 51-58, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein each  $R^2$  is independently  $C_{1-6}$ alkyl.

60. The compound of any one of claims 51-59, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein q is 2.

61. The compound of any one of claims 51-59, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein q is 1.

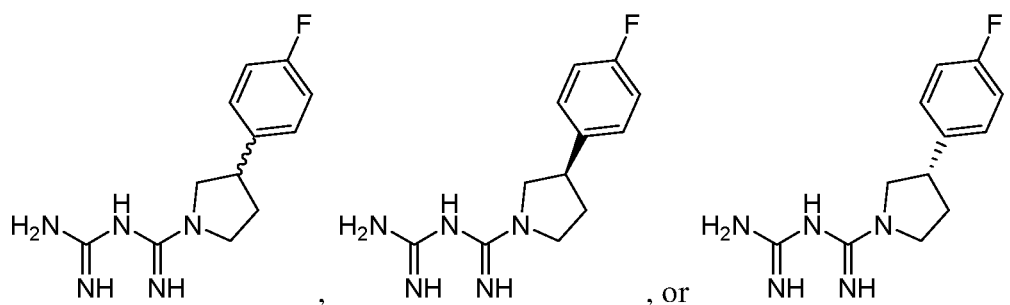
62. The compound of any one of claims 51-57, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein q is 0.

63. A compound having the structure:



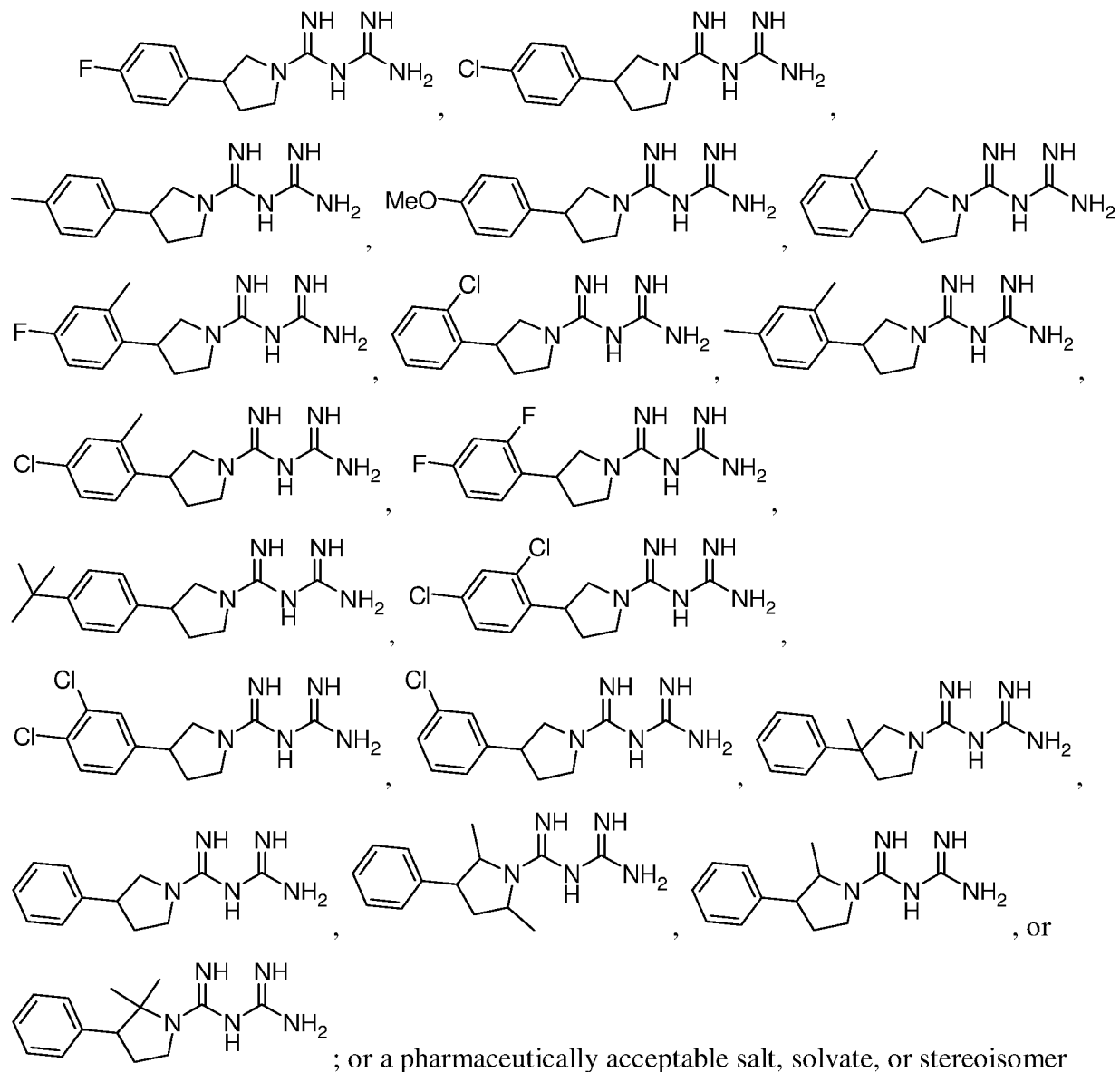
or a pharmaceutically acceptable salt or solvate thereof.

64. A compound having the structure:



or a pharmaceutically acceptable salt or solvate thereof.

65. A compound having the structure:



thereof.

66. A pharmaceutical composition comprising a compound of any one of claims 1-65, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient.

67. A method of treating cancer in a subject, comprising administering to a subject a therapeutically effective amount of a compound of any one of claims 1-65, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

68. The method of claim 67, wherein the cancer is selected from IDH1 mutant cancers and cancers with LKB1 deficient tumors.

69. A method of treating diabetes in a subject, comprising administering to a subject a therapeutically effective amount of a compound of any one of claims 1-65, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

70. The method of claim 69, wherein the diabetes is type 2 diabetes.

71. A method of treating polycystic ovarian syndrome in a subject, comprising administering to a subject a therapeutically effective amount of a compound of any one of claims 1-65, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

72. The method of any one of claims 67-71, further comprising the administration of a second therapeutic agent.

73. The method of claim 72, wherein the second therapeutic agent is a BRAF inhibitor.

74. The method of claim 73, wherein the BRAF inhibitor is selected from dabrafenib, vemurafenib, encorafenib, TAK-580, LY3009120, BGB-283, HM955573, and PLX8394.

75. The method of claim 72, wherein the second therapeutic agent is an mTOR inhibitor.

76. The method of claim 75, wherein the mTOR inhibitor is selected from everolimus, TAK-228, AZD2014, LY3023414, and gedatolisib.

FIGURE 1

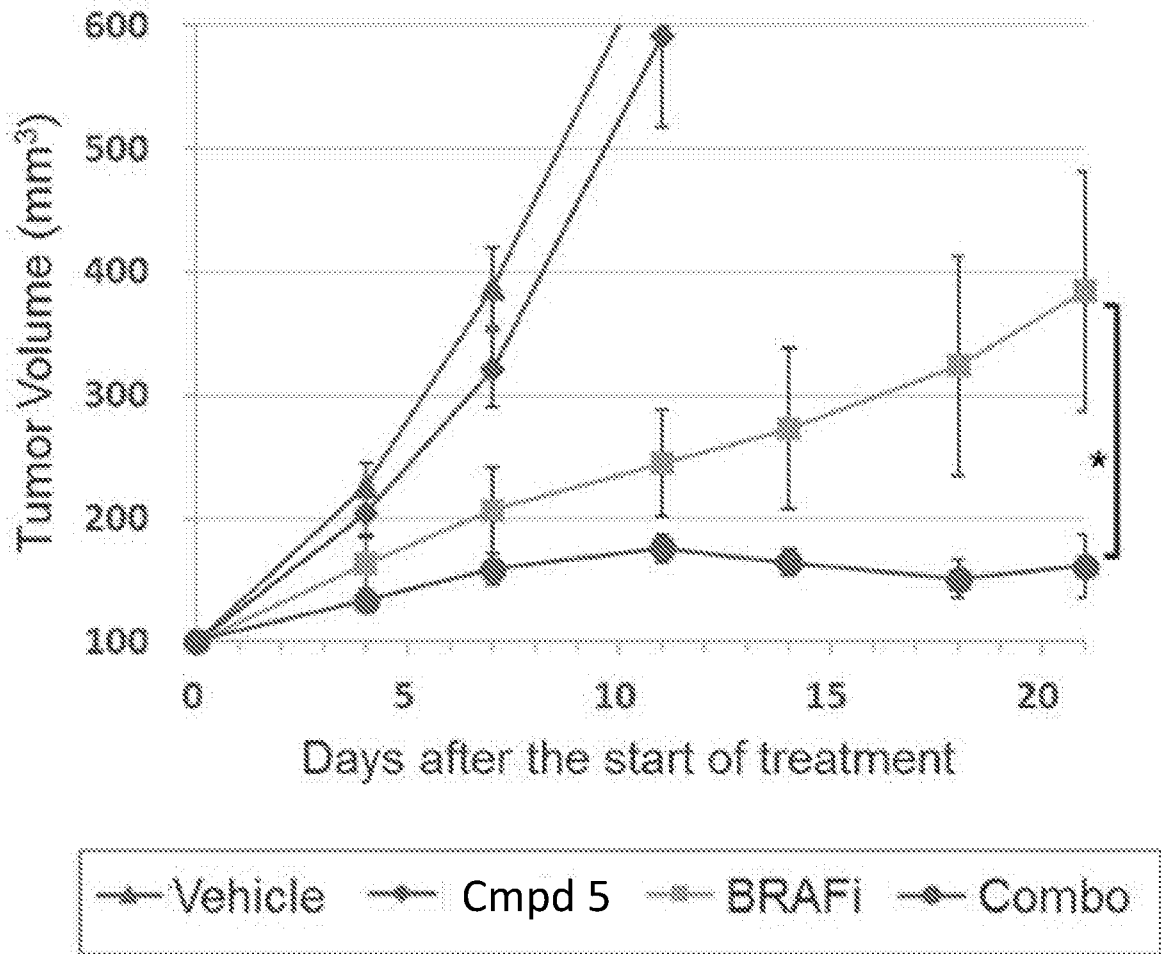
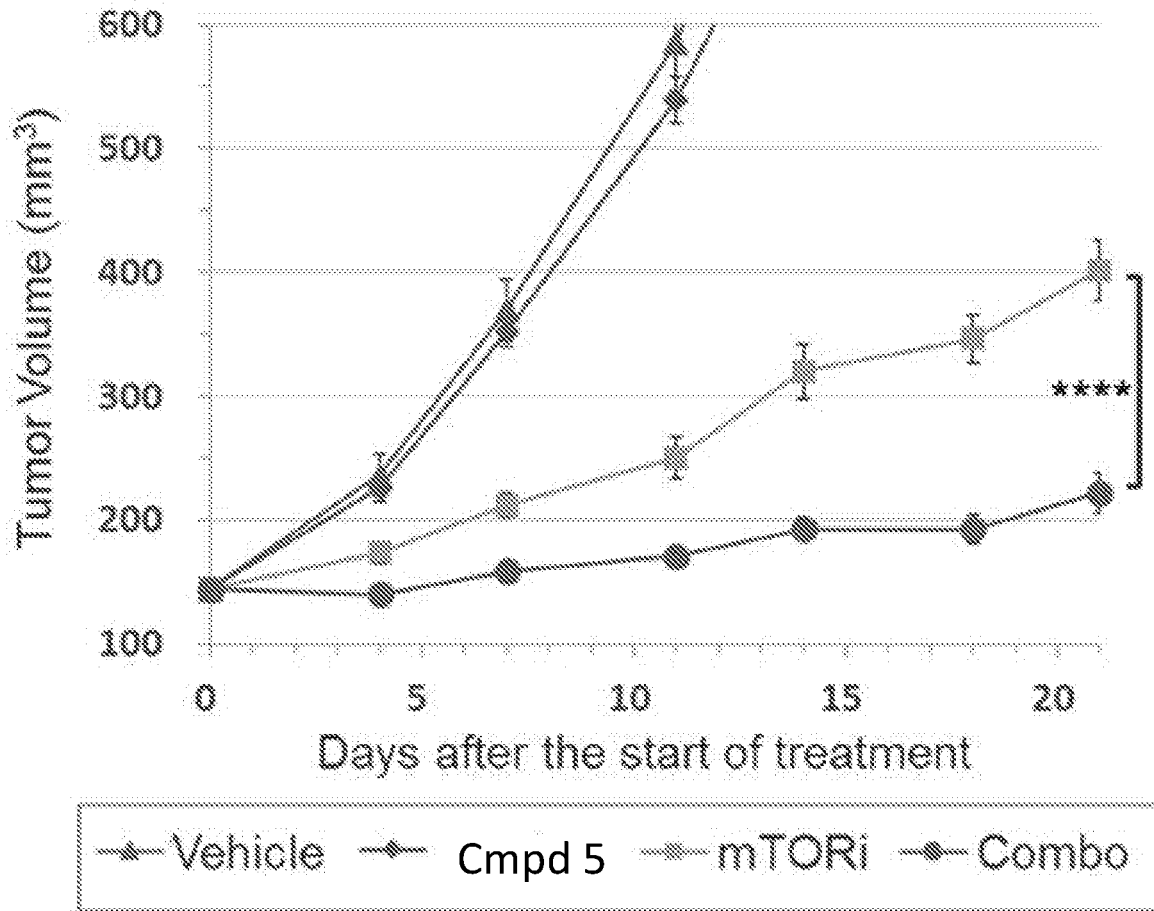


FIGURE 2



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/35720

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

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

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.: 4-11, 13-17, 21-33, 37-50, 54-62, 66-76  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

--please see supplemental box --

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
Claims 1-3, 12 and 63-65

- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/35720

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC(8) - A61K 31/155, A61K 45/06, A61K 31/137, A61K 31/485, A61K 9/20 (2017.01)  
 CPC - A61K 31/7048, A61K 9/2018, A61K 9/2846, A61K 9/209, A61K 9/2054, A61K 31/155, A61K 31/137

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

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

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

See Search History Document

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

See Search History Document

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2015/0064223 A1 (Baron et al.) 05 March 2015 (05.03.2015) entire document especially para [0009]; page 12, col 1, last compounds	1-3, 12 and 63-65
A	US 5,254,593 A (Ulrich et al.) 19 October 1993 (19.10.1993) entire document especially claim 1	1-3, 12 and 63-65
A	US 2014/0341986 A1 (Baron et al.) 20 November 2014 (20.11.2014) entire document especially para [0009]; page 166, col 1, last compounds	1-3, 12 and 63-65
A	US 2008/0292568 A1 (Tobia et al.) 27 November 2008 (27.11.2008) entire document	1-3, 12 and 63-65
A	US 8,541,474 B2 (Kim et al.) 24 September 2013 (24.09.2013) entire document	1-3, 12 and 63-65
A	US 7,563,792 B2 (Jacobus et al.) 21 July 2009 (21.07.2009) entire document	1-3, 12 and 63-65
A	WO 2000/062626 A1 (Fox Chase Cancer Center) 26 October 2000 (26.10.2000) entire document	1-3, 12 and 63-65
A	WO 2013/022280 A2 (Hanall Biopharma Co., Ltd.) 14 February 2013 (14.02.2013) entire document	1-3, 12 and 63-65

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

18 September 2017

Date of mailing of the international search report

05 OCT 2017

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents  
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 Facsimile No. 571-273-8300

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300  
 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/35720

Continuation of Box No. III, Observations where unity of invention is lacking:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-3, 12 and 63-65, directed to a compound of formula (I)

Group II: Claims 18-20 directed to a compound of formula (II)

Group III: Claims 34-36 directed to a compound of formula (III)

Group IV: Claims 51-53, directed to a compound of formula (IV)

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I requires a compound of formula (I), not required by groups II-IV

Groups II requires compound of formula (II), not required by groups I and III-IV

Groups III requires compound of formula (III), not required by groups I-II and IV

Group IV requires a compound of formula (IV), not required by groups I-III

Common Technical Features:

Groups I-IV share the technical feature of metformin derivative.

However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by US 2010/0087544 A1 to Kim et al. (hereafter 'Kim'). Kim teaches metformin derivative (para [0054])

As the shared technical features were known in the art at the time of the invention, they cannot be considered common technical features that would otherwise unify the groups. Therefore, Groups I-IV lack unity under PCT Rule 13.