

## SOLID FORMS OF AN ORALLY-DELIVERED BETA-LACTAMASE INHIBITOR AND USES THEREOF

### CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application Serial No. 62/828,349 filed April 2, 2019, which is hereby incorporated by reference in its entirety.

### STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with government support under Grant number R43AI109879 awarded by the National Institutes of Health (NIH), Grant number R44AI109879 awarded by the National Institutes of Health (NIH), Grant number R01AI111539 awarded by the National Institutes of Health (NIH), and Contract number HHSN272201600029C awarded by the National Institutes of Health (NIH). The government has certain rights in the invention.

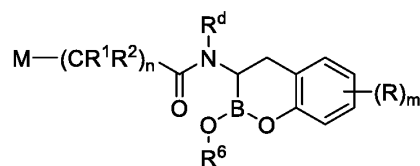
### BACKGROUND OF THE INVENTION

[0003] Antibiotics are the most effective drugs for treating bacteria-infectious diseases. They are largely used in the clinic because of their good antibacterial effect with limited side effects. Among them, the beta-lactam class of antibiotics (for example, penicillins, cephalosporins, monobactams and carbapenems) are preferred because their effect is bactericidal, and their target is absent in eukaryotic cells with consequent low toxicity.

[0004] To counter the efficacy of the various beta-lactams, bacteria have evolved to produce variants of beta-lactam deactivating enzymes called beta-lactamases, and in the ability to share this tool both vertically and horizontally inter- and intra-species. These beta-lactamases are categorized as “serine” or “metallo” based, respectively, based on the presence of a key serine or zinc in the enzyme active site. The rapid induction, selection and spread of this mechanism of bacterial resistance can severely limit the whole class of beta-lactam treatment options in the hospital and in the community. There is a need for effective and safe therapeutic agents that can treat such resistant infections.

### SUMMARY OF THE INVENTION

[0005] Disclosed herein is a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (I)

wherein:

M is hydrogen, halogen,  $-\text{CD}_3$ ,  $-\text{CF}_3$ ,  $-\text{CN}$ ,  $-\text{OR}^4$ ,  $-\text{C}(=\text{O})\text{R}^4$ ,  $-\text{C}(=\text{O})\text{NR}^4\text{R}^5$ ,  $-\text{SR}^4$ ,  $-\text{S}(=\text{O})\text{R}^4$ ,  $-\text{S}(=\text{O})_2\text{R}^4$ ,  $-\text{S}(=\text{O})_2\text{NR}^4\text{R}^5$ ,  $-\text{NR}^4\text{R}^5$ ,  $-\text{NR}^4\text{C}(=\text{O})\text{R}^5$ ,  $-\text{NR}^4\text{C}(=\text{O})\text{NR}^4\text{R}^5$ ,  $-\text{NR}^4\text{S}(=\text{O})_2\text{R}^5$ , or alkynyl;

each  $\text{R}^1$  and  $\text{R}^2$  is independently hydrogen, deuterium, halogen,  $-\text{OR}^4$ ,  $-\text{SR}^4$ ,  $-\text{NR}^4\text{R}^5$ , optionally substituted  $\text{C}_1\text{-C}_6$  alkyl, optionally substituted  $\text{C}_1\text{-C}_6$  haloalkyl, optionally substituted  $\text{C}_1\text{-C}_6$  hydroxyalkyl, or optionally substituted  $\text{C}_1\text{-C}_6$  aminoalkyl;

or  $\text{R}^1$  and  $\text{R}^2$  are taken together with the carbon to which they are attached to form an optionally substituted cycloalkyl;

or when n is at least 2, two  $\text{R}^1$  on adjacent carbons are taken together to form a double bond;

or when n is at least 2, two  $\text{R}^1$  and two  $\text{R}^2$  on adjacent carbons are taken together to form a triple bond;

n is 0, 1, 2, 3, 4, 5, or 6;

each R is independently  $-\text{COOR}^3$ ,  $\text{R}^a$ ,  $\text{R}^b$ , or  $\text{R}^c$ ;

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

$\text{R}^3$  is  $\text{R}^{31}$ ,  $-(\text{R}^{30})_q\text{OR}^{31}$ ,  $-(\text{R}^{30})_q\text{O}(\text{R}^{30})_q\text{OR}^{31}$ ,  $-\text{R}^{30}\text{OC}(\text{O})\text{R}^{31}$ ,  $-\text{R}^{30}\text{OC}(\text{O})\text{OR}^{31}$ ,  $-\text{R}^{30}\text{OC}(\text{O})\text{NHR}^{31}$ , or  $-\text{R}^{30}\text{OC}(\text{O})\text{N}(\text{R}^{31})_2$ ;

each q is independently 2, 3, 4, 5, or 6;

each  $\text{R}^{30}$  is independently  $-\text{CH}_2-$ ,  $-\text{CH}(\text{CH}_3)-$ ,  $-\text{C}(\text{CH}_3)_2-$ , or optionally substituted 1,1-cyclopropylene;

each  $\text{R}^{31}$  is independently optionally substituted  $\text{C}_1\text{-C}_{12}$  alkyl, optionally substituted  $\text{C}_1\text{-C}_{12}$  haloalkyl, optionally substituted  $\text{C}_1\text{-C}_{12}$  hydroxyalkyl, optionally substituted  $\text{C}_1\text{-C}_{12}$  aminoalkyl, optionally substituted  $\text{C}_1\text{-C}_{12}$  alkoxyalkyl, optionally substituted  $\text{C}_2\text{-C}_{12}$  alkenyl, optionally substituted  $\text{C}_2\text{-C}_{12}$  alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted  $(\text{C}_1\text{-C}_6 \text{ alkyl})\text{cycloalkyl}$ , optionally substituted  $(\text{C}_1\text{-C}_6 \text{ alkyl})\text{heterocycloalkyl}$ , optionally substituted  $(\text{C}_1\text{-C}_6 \text{ alkyl})\text{aryl}$ , or optionally substituted  $(\text{C}_1\text{-C}_6 \text{ alkyl})\text{heteroaryl}$ ; or

two  $\text{R}^{31}$  are taken together with the nitrogen to which they are attached to form a heterocycloalkyl;

$\text{R}^a$ ,  $\text{R}^b$ , and  $\text{R}^c$  are independently hydrogen, deuterium, halogen,  $-\text{OR}^4$ ,  $-\text{NR}^4\text{R}^5$ ,  $-\text{SR}^4$ , optionally substituted  $\text{C}_1\text{-C}_6$  alkyl, optionally substituted  $\text{C}_1\text{-C}_6$  haloalkyl, optionally substituted  $\text{C}_1\text{-C}_6$  hydroxyalkyl, optionally substituted  $\text{C}_1\text{-C}_6$  aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

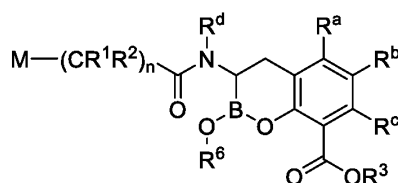
$\text{R}^d$  is hydrogen or optionally substituted  $\text{C}_1\text{-C}_6$  alkyl;

$\text{R}^4$  and  $\text{R}^5$  are independently hydrogen,  $-\text{OH}$ ,  $-\text{CN}$ , optionally substituted  $\text{C}_1\text{-C}_6$  alkyl, optionally substituted  $\text{C}_1\text{-C}_6$  haloalkyl, optionally substituted  $\text{C}_1\text{-C}_6$  hydroxyalkyl, optionally substituted  $\text{C}_1\text{-C}_6$  aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

or  $\text{R}^4$  and  $\text{R}^5$  taken together with the nitrogen to which they are attached to form an optionally substituted heterocycloalkyl; and

R<sup>6</sup> is optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted C<sub>1</sub>-C<sub>6</sub> haloalkyl, optionally substituted C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, optionally substituted C<sub>1</sub>-C<sub>6</sub> aminoalkyl, optionally substituted C<sub>1</sub>-C<sub>6</sub> deutoalkyl, optionally substituted C<sub>1</sub>-C<sub>6</sub> heteroalkyl, optionally substituted C<sub>2</sub>-C<sub>6</sub> alkenyl, optionally substituted C<sub>2</sub>-C<sub>6</sub> alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted (C<sub>1</sub>-C<sub>6</sub> alkyl)cycloalkyl, optionally substituted (C<sub>1</sub>-C<sub>6</sub> alkyl)heterocycloalkyl, optionally substituted (C<sub>1</sub>-C<sub>6</sub> alkyl)aryl, or optionally substituted (C<sub>1</sub>-C<sub>6</sub> alkyl)heteroaryl.

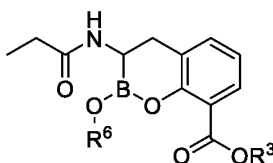
[0006] In some embodiments of a compound of Formula (I), the compound is of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (Ia).

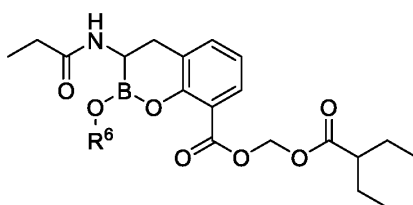
[0007] In some embodiments of a compound of Formula (I) or (Ia), R<sup>a</sup>, R<sup>b</sup>, and R<sup>c</sup> are independently hydrogen, halogen, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>5</sup>, -SR<sup>4</sup>, or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl. In some embodiments of a compound of Formula (I) or (Ia), R<sup>a</sup>, R<sup>b</sup>, and R<sup>c</sup> are independently hydrogen, halogen, -OH, or -OCH<sub>3</sub>. In some embodiments of a compound of Formula (I) or (Ia), R<sup>a</sup>, R<sup>b</sup>, and R<sup>c</sup> are hydrogen. In some embodiments of a compound of Formula (I) or (Ia), R<sup>d</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl. In some embodiments of a compound of Formula (I) or (Ia), R<sup>d</sup> is hydrogen.

[0008] In some embodiments of a compound of Formula (I) or (Ia), n is 0, 1, 2, or 3. In some embodiments of a compound of Formula (I) or (Ia), n is 2. In some embodiments of a compound of Formula (I) or (Ia), n is 1. In some embodiments of a compound of Formula (I) or (Ia), each R<sup>1</sup> and R<sup>2</sup> are independently hydrogen, halogen, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or optionally substituted C<sub>1</sub>-C<sub>6</sub> haloalkyl. In some embodiments of a compound of Formula (I) or (Ia), each R<sup>1</sup> and R<sup>2</sup> are independently hydrogen or halogen. In some embodiments of a compound of Formula (I) or (Ia), each R<sup>1</sup> and R<sup>2</sup> are hydrogen. In some embodiments of a compound of Formula (I) or (Ia), M is hydrogen, -CN, -C(=O)R<sup>4</sup>, or alkynyl. In some embodiments of a compound of Formula (I) or (Ia), M is hydrogen. In some embodiments of a compound of Formula (I) or (Ia), the compound is of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (Ib).

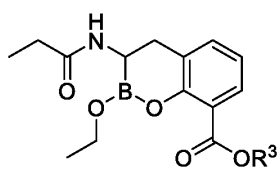
[0009] In some embodiments of a compound of Formula (I) or (Ia) or (Ib),  $R^3$  is  $R^{31}$ . In some embodiments of a compound of Formula (I) or (Ia) or (Ib),  $R^3$  is  $-R^{30}OC(O)R^{31}$  or  $-R^{30}OC(O)OR^{31}$ . In some embodiments of a compound of Formula (I) or (Ia) or (Ib),  $R^3$  is  $-R^{30}OC(O)R^{31}$ . In some embodiments of a compound of Formula (I) or (Ia) or (Ib),  $R^{30}$  is independently  $-CH_2-$  or  $-CH(CH_3)-$ . In some embodiments of a compound of Formula (I) or (Ia) or (Ib),  $R^{30}$  is independently  $-CH_2-$ . In some embodiments of a compound of Formula (I) or (Ia) or (Ib), each  $R^{31}$  is independently optionally substituted  $C_1$ - $C_{12}$  alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted aryl. In some embodiments of a compound of Formula (I) or (Ia) or (Ib), each  $R^{31}$  is independently optionally substituted  $C_1$ - $C_{12}$  alkyl. In some embodiments of a compound of Formula (I) or (Ia) or (Ib), the compound is of Formula (Ic), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



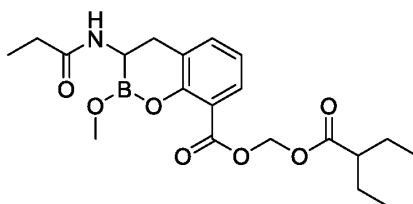
Formula (Ic).

[0010] In some embodiments of a compound of Formula (I) or (Ia) or (Ib) or (Ic),  $R^6$  is  $C_1$ - $C_6$  alkyl. In some embodiments of a compound of Formula (I) or (Ia) or (Ib) or (Ic),  $R^6$  is methyl, ethyl, propyl, or butyl.

[0011] In some embodiments of a compound of Formula (I) or (Ia) or (Ib), the compound is of Formula (Id), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



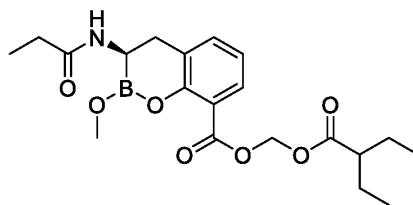
Formula (Id). In some embodiments of a compound of Formula (I) or (Ia)



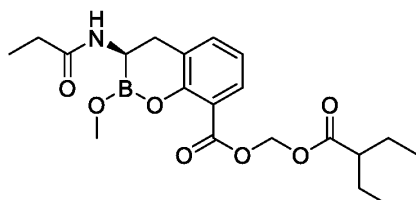
or (Ib) or (Ic), the compound is:

or a pharmaceutically

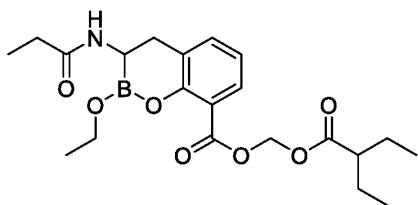
acceptable salt, solvate, or stereoisomer thereof. In some embodiments of a compound of Formula (I)



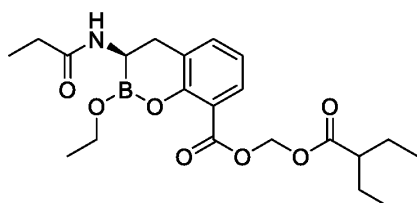
or (Ia) or (Ib) or (Ic), the compound is: or a pharmaceutically acceptable salt or solvate thereof. In some embodiments of a compound of Formula (I) or (Ia) or (Ib)



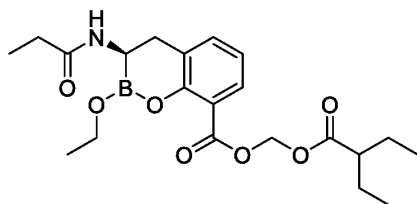
or (Ic), the compound is: . In some embodiments of a compound of Formula (I) or (Ia) or (Ib) or (Ic), the compound is:



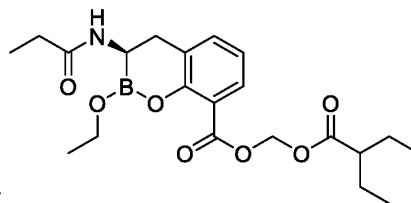
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments of a compound of Formula (I) or (Ia) or (Ib) or (Ic), the



compound is: or a pharmaceutically acceptable salt or solvate thereof. In some embodiments of a compound of Formula (I) or (Ia) or (Ib) or (Ic), the



compound is:



**[0012]** Also disclosed herein is a crystalline form of some embodiment, the crystalline form has an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in FIG. 4. In some embodiment, the crystalline form has an X-ray powder diffraction (XRPD) pattern comprising characteristic peaks at about  $6.1^{\circ} \pm 0.1^{\circ} 2\theta$ , about  $9.9^{\circ} \pm 0.1^{\circ}$

2 $\theta$ , and about 16.0 ° $\pm$ 0.1° 2 $\theta$ . In some embodiment, the X-ray powder diffraction (XRPD) pattern further comprises characteristic peaks at about 19.3 ° $\pm$ 0.1° 2 $\theta$ , about 6.8 ° $\pm$ 0.1° 2 $\theta$ , and about 17.9 ° $\pm$ 0.1° 2 $\theta$ . In some embodiments, the X-ray powder diffraction (XRPD) pattern further comprises characteristic peaks at about 14.3 ° $\pm$ 0.1° 2 $\theta$  and about 21.2 ° $\pm$ 0.1° 2 $\theta$ . In some embodiment, the crystalline form has a DSC thermogram substantially the same as shown in FIG. 6. In some embodiment, the crystalline form has a DSC thermogram with a broad endotherm having an onset at about 112.8 °C. In some embodiment, the crystalline form has a <sup>1</sup>H spectrum substantially the same as shown in FIG. 1A. In some embodiment, the crystalline form has a <sup>13</sup>C spectrum substantially the same as shown in FIG. 1B. In some embodiment, the crystalline form has an FT-IR spectrum substantially the same as shown in FIG. 2. In some embodiment, the crystalline form has a Raman spectrum substantially the same as shown in FIG. 3.

[0013] In some embodiment, the crystalline form has an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in FIG. 10. In some embodiment, the crystalline form has an X-ray powder diffraction (XRPD) pattern comprising characteristic peaks at about 9.3 ° $\pm$ 0.1° 2 $\theta$ , about 12.9 ° $\pm$ 0.1° 2 $\theta$ , and about 21.5 ° $\pm$ 0.1° 2 $\theta$ . In some embodiment, the X-ray powder diffraction (XRPD) pattern further comprises characteristic peaks at about 8.8 ° $\pm$ 0.1° 2 $\theta$ , about 14.6 ° $\pm$ 0.1° 2 $\theta$ , and about 17.3 ° $\pm$ 0.1° 2 $\theta$ . In some embodiment, the crystalline form has a DSC thermogram substantially the same as shown in FIG. 11. In some embodiment, the crystalline form has a DSC thermogram with a broad endotherm having an onset at about 116.9 °C. In some embodiment, the crystalline form has an FT-Raman spectrum substantially the same as shown in FIG. 9A.

[0014] Also disclosed herein is a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable excipient. In some embodiment, the pharmaceutical composition further comprises a beta-lactam antibiotic. In some embodiment, the beta-lactam antibiotic is a penicillin, a cephalosporin, a carbapenem, a monobactam, or a combination thereof.

[0015] Also disclosed herein is a method of treating a bacterial infection in a subject, comprising administering to the subject a compound disclosed herein in combination with a therapeutically effective amount of a beta-lactam antibiotic. In some embodiment, the beta-lactam antibiotic is ceftibuten, or a salt thereof.

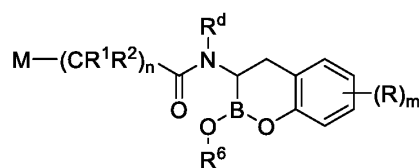
#### BRIEF DESCRIPTION OF THE DRAWINGS

- [0016] FIG. 1A shows the <sup>1</sup>H NMR spectrum for Compound 1-ethanolate Form A (in CD<sub>2</sub>Cl<sub>2</sub>).
- [0017] FIG. 1B shows the <sup>13</sup>C NMR spectrum for Compound 1-ethanolate Form A (in CD<sub>2</sub>Cl<sub>2</sub>).
- [0018] FIG. 2 shows the FT-IR spectrum for Compound 1-ethanolate Form A.
- [0019] FIG. 3 shows the FT-Raman spectrum for Compound 1-ethanolate Form A.
- [0020] FIG. 4 shows the XRPD pattern for Compound 1-ethanolate Form A.
- [0021] FIG. 5 shows the indexing solution for Compound 1-ethanolate Form A with Cu-K $\alpha$  radiation.

- [0022] FIG. 6 shows the DSC thermogram of Compound 1-ethanolate Form A.
- [0023] FIG. 7 shows the DVS analysis of Compound 1-ethanolate Form A (weight% vs. relative humidity).
- [0024] FIG. 8 shows an overlay of FT-IR Spectra for Compound 1-ethanolate Forms. Top: Form B; Bottom, Form A.
- [0025] FIG. 9A shows the FT-Raman spectrum for Compound 1-ethanolate Form B.
- [0026] FIG. 9B shows an overlay of Raman Spectra for Compound 1-ethanolate Forms. Top: Form B; Bottom, Form A.
- [0027] FIG. 10 shows the indexing solution for Compound 1-ethanolate Form B, with Cu-K $\alpha$  radiation.
- [0028] FIG. 11 shows the DSC thermogram of Compound 1-ethanolate Form B.
- [0029] FIG. 12 shows the DVS analysis of Compound 1-ethanolate Form B (weight% vs. relative humidity).
- [0030] FIG. 13 shows the x-ray structure of Compound 1-methanolate.
- [0031] FIG. 14A shows the optical microscopy image of Compound 1-ethanolate Form A recorded without crossed polarizers. The sample clearly has a needle-like morphology.
- [0032] FIG. 14B shows optical microscopy images of Compound 1-ethanolate Form A recorded with crossed polarizers. The sample clearly has a needle-like morphology.
- [0033] FIG. 15A shows the optical microscopy image of Compound 1-ethanolate Form B recorded without crossed polarizers. The sample generally has a plate-like morphology.
- [0034] FIG. 15B shows optical microscopy images of Compound 1-ethanolate Form B recorded with crossed polarizers. The sample generally has a plate-like morphology.

### DETAILED DESCRIPTION

[0035] Disclosed herein a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (I)

wherein:

M is hydrogen, halogen, -CD<sub>3</sub>, -CF<sub>3</sub>, -CN, -OR<sup>4</sup>, -C(=O)R<sup>4</sup>, -C(=O)NR<sup>4</sup>R<sup>5</sup>, -SR<sup>4</sup>, -S(=O)R<sup>4</sup>, -S(=O)<sub>2</sub>R<sup>4</sup>, -S(=O)<sub>2</sub>NR<sup>4</sup>R<sup>5</sup>, -NR<sup>4</sup>R<sup>5</sup>, -NR<sup>4</sup>C(=O)R<sup>5</sup>, -NR<sup>4</sup>C(=O)NR<sup>4</sup>R<sup>5</sup>, -NR<sup>4</sup>S(=O)<sub>2</sub>R<sup>5</sup>, or alkynyl;

each  $R^1$  and  $R^2$  is independently hydrogen, deuterium, halogen,  $-OR^4$ ,  $-SR^4$ ,  $-NR^4R^5$ , optionally substituted  $C_1-C_6$  alkyl, optionally substituted  $C_1-C_6$  haloalkyl, optionally substituted  $C_1-C_6$  hydroxyalkyl, or optionally substituted  $C_1-C_6$  aminoalkyl;

or  $R^1$  and  $R^2$  are taken together with the carbon to which they are attached to form an optionally substituted cycloalkyl;

or when  $n$  is at least 2, two  $R^1$  on adjacent carbons are taken together to form a double bond;

or when  $n$  is at least 2, two  $R^1$  and two  $R^2$  on adjacent carbons are taken together to form a triple bond;

$n$  is 0, 1, 2, 3, 4, 5, or 6;

each  $R$  is independently  $-COOR^3$ ,  $R^a$ ,  $R^b$ , or  $R^c$ ;

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

$R^3$  is  $R^{31}$ ,  $-(R^{30})_qOR^{31}$ ,  $-(R^{30})_qO(R^{30})_qOR^{31}$ ,  $-R^{30}OC(O)R^{31}$ ,  $-R^{30}OC(O)OR^{31}$ ,  $-R^{30}OC(O)NHR^{31}$ , or  $-R^{30}OC(O)N(R^{31})_2$ ;

each  $q$  is independently 2, 3, 4, 5, or 6;

each  $R^{30}$  is independently  $-CH_2-$ ,  $-CH(CH_3)-$ ,  $-C(CH_3)_2-$ , or optionally substituted 1,1-cyclopropylene;

each  $R^{31}$  is independently optionally substituted  $C_1-C_{12}$  alkyl, optionally substituted  $C_1-C_{12}$  haloalkyl, optionally substituted  $C_1-C_{12}$  hydroxyalkyl, optionally substituted  $C_1-C_{12}$  aminoalkyl, optionally substituted  $C_1-C_{12}$  alkoxyalkyl, optionally substituted  $C_2-C_{12}$  alkenyl, optionally substituted  $C_2-C_{12}$  alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted  $(C_1-C_6 \text{ alkyl})$ cycloalkyl, optionally substituted  $(C_1-C_6 \text{ alkyl})$ heterocycloalkyl, optionally substituted  $(C_1-C_6 \text{ alkyl})$ aryl, or optionally substituted  $(C_1-C_6 \text{ alkyl})$ heteroaryl; or

two  $R^{31}$  are taken together with the nitrogen to which they are attached to form a heterocycloalkyl;

$R^a$ ,  $R^b$ , and  $R^c$  are independently hydrogen, deuterium, halogen,  $-OR^4$ ,  $-NR^4R^5$ ,  $-SR^4$ , optionally substituted  $C_1-C_6$  alkyl, optionally substituted  $C_1-C_6$  haloalkyl, optionally substituted  $C_1-C_6$  hydroxyalkyl, optionally substituted  $C_1-C_6$  aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

$R^d$  is hydrogen or optionally substituted  $C_1-C_6$  alkyl;

$R^4$  and  $R^5$  are independently hydrogen,  $-OH$ ,  $-CN$ , optionally substituted  $C_1-C_6$  alkyl, optionally substituted  $C_1-C_6$  haloalkyl, optionally substituted  $C_1-C_6$  hydroxyalkyl, optionally substituted  $C_1-C_6$  aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

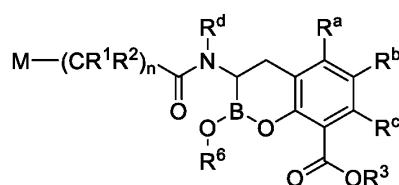
or  $R^4$  and  $R^5$  taken together with the nitrogen to which they are attached to form an optionally substituted heterocycloalkyl; and

$R^6$  is optionally substituted  $C_1-C_6$  alkyl, optionally substituted  $C_1-C_6$  haloalkyl, optionally substituted  $C_1-C_6$  hydroxyalkyl, optionally substituted  $C_1-C_6$  aminoalkyl, optionally substituted  $C_1-C_6$

deuteroalkyl, optionally substituted C<sub>1</sub>-C<sub>6</sub> heteroalkyl, optionally substituted C<sub>2</sub>-C<sub>6</sub> alkenyl, optionally substituted C<sub>2</sub>-C<sub>6</sub> alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted (C<sub>1</sub>-C<sub>6</sub> alkyl)cycloalkyl, optionally substituted (C<sub>1</sub>-C<sub>6</sub> alkyl)heterocycloalkyl, optionally substituted (C<sub>1</sub>-C<sub>6</sub> alkyl)aryl, or optionally substituted (C<sub>1</sub>-C<sub>6</sub> alkyl)heteroaryl.

**[0036]** In some embodiments of a compound of Formula (I), m is 1, 2, 3, or 4. In some embodiments of a compound of Formula (I), m is 1, 2, or 3. In some embodiments of a compound of Formula (I), m is 1 or 2.

**[0037]** In some embodiments of a compound of Formula (I), the compound is of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (Ia).

**[0038]** In some embodiments of a compound of Formula (I) or (Ia), R<sup>a</sup>, R<sup>b</sup>, and R<sup>c</sup> are independently hydrogen, halogen, -OR<sup>4</sup>, -NR<sup>4</sup>R<sup>5</sup>, -SR<sup>4</sup>, or optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl. In some embodiments of a compound of Formula (I) or (Ia), R<sup>a</sup>, R<sup>b</sup>, and R<sup>c</sup> are independently hydrogen, halogen, -OH, or -OCH<sub>3</sub>. In some embodiments of a compound of Formula (I) or (Ia), R<sup>a</sup>, R<sup>b</sup>, and R<sup>c</sup> are hydrogen.

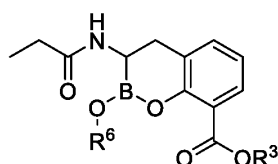
**[0039]** In some embodiments of a compound of Formula (I) or (Ia), R<sup>d</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl. In some embodiments of a compound of Formula (I) or (Ia), R<sup>d</sup> is hydrogen.

**[0040]** In some embodiments of a compound of Formula (I) or (Ia), n is 0, 1, 2, or 3. In some embodiments of a compound of Formula (I) or (Ia), n is 1 or 2. In some embodiments of a compound of Formula (I) or (Ia), n is 2. In some embodiments of a compound of Formula (I) or (Ia), n is 1.

**[0041]** In some embodiments of a compound of Formula (I) or (Ia), each R<sup>1</sup> and R<sup>2</sup> are independently hydrogen, halogen, optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, or optionally substituted C<sub>1</sub>-C<sub>6</sub> haloalkyl. In some embodiments of a compound of Formula (I) or (Ia), each R<sup>1</sup> and R<sup>2</sup> are independently hydrogen or halogen. In some embodiments of a compound of Formula (I) or (Ia), each R<sup>1</sup> and R<sup>2</sup> are hydrogen.

**[0042]** In some embodiments of a compound of Formula (I) or (Ia), M is hydrogen, halogen, -CF<sub>3</sub>, -CN, -OR<sup>4</sup>, -C(=O)R<sup>4</sup>, -SR<sup>4</sup>, or alkynyl. In some embodiments of a compound of Formula (I) or (Ia), M is hydrogen, -CN, -OR<sup>4</sup>, -C(=O)R<sup>4</sup>, -SR<sup>4</sup>, or alkynyl. In some embodiments of a compound of Formula (I) or (Ia), M is hydrogen, -CN, -C(=O)R<sup>4</sup>, or alkynyl. In some embodiments of a compound of Formula (I) or (Ia), M is hydrogen. In some embodiments of a compound of Formula (I) or (Ia), M is hydrogen.

[0043] In some embodiments of a compound of Formula (I) or (Ia), the compound is of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:

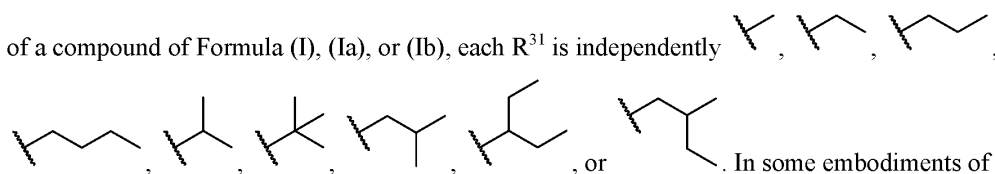


Formula (Ib).

[0044] In some embodiments of a compound of Formula (I), (Ia), or (Ib),  $R^3$  is  $R^{31}$ . In some embodiments of a compound of Formula (I), (Ia), or (Ib),  $R^3$  is  $-R^{30}OC(O)R^{31}$  or  $-R^{30}OC(O)OR^{31}$ . In some embodiments of a compound of Formula (I), (Ia), or (Ib),  $R^3$  is  $-R^{30}OC(O)R^{31}$ .

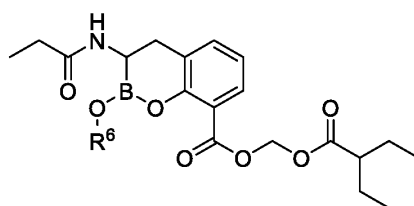
[0045] In some embodiments of a compound of Formula (I), (Ia), or (Ib),  $R^{30}$  is independently  $-CH_2-$  or  $-CH(CH_3)-$ . In some embodiments of a compound of Formula (I), (Ia), or (Ib),  $R^{30}$  is independently  $-CH_2-$ .

[0046] In some embodiments of a compound of Formula (I), (Ia), or (Ib), each  $R^{31}$  is independently optionally substituted  $C_1$ - $C_{12}$  alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted aryl. In some embodiments of a compound of Formula (I), (Ia), or (Ib), each  $R^{31}$  is independently optionally substituted  $C_1$ - $C_{12}$  alkyl. In some embodiments of a compound of Formula (I), (Ia), or (Ib), each  $R^{31}$  is independently  $C_1$ - $C_{12}$  alkyl. In some embodiments of a compound of Formula (I), (Ia), or (Ib), each  $R^{31}$  is independently



compound of Formula (I), (Ia), or (Ib), each  $R^{31}$  is

[0047] In some embodiments of a compound of Formula (I), (Ia), or (Ib), the compound is of Formula (Ic), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (Ic).

[0048] In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Ic),  $R^6$  is  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  hydroxyalkyl,  $C_1$ - $C_6$  aminoalkyl,  $C_1$ - $C_6$  deuterioalkyl,  $C_1$ - $C_6$  heteroalkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl, cycloalkyl, heterocycloalkyl,  $(C_1$ - $C_6$  alkyl)cycloalkyl,  $(C_1$ - $C_6$

alkyl)heterocycloalkyl, (C<sub>1</sub>-C<sub>6</sub> alkyl)aryl, or (C<sub>1</sub>-C<sub>6</sub> alkyl)heteroaryl; each optionally substituted with deuterium, halogen, -OH, -OMe, -COMe, -COOH, -COOMe, NH<sub>2</sub>, -NHMe, NMe<sub>2</sub>, cycloalkyl, or heterocycloalkyl.

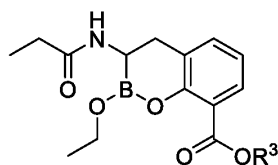
**[0049]** In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Ic), R<sup>6</sup> is optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted cycloalkyl, or optionally substituted heterocycloalkyl.

**[0050]** In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Ic), R<sup>6</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with deuterium, halogen, -OH, -OMe, -COOH, -COOMe, NH<sub>2</sub>, -NHMe, or NMe<sub>2</sub>. In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Ic), R<sup>6</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with -OH.

**[0051]** In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Ic), R<sup>6</sup> is cycloalkyl optionally substituted with deuterium, halogen, -OH, -OMe, -COOH, -COOMe, NH<sub>2</sub>, -NHMe, NMe<sub>2</sub>, -CH<sub>2</sub>OH, or -CH<sub>2</sub>OMe. In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Ic), R<sup>6</sup> is cycloalkyl optionally substituted with halogen, -OH or -CH<sub>2</sub>OH.

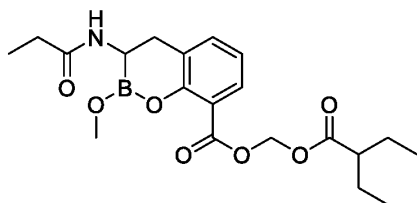
**[0052]** In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Ic), R<sup>6</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl. In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Ic), R<sup>6</sup> is methyl, ethyl, propyl, or butyl. In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Ic), R<sup>6</sup> is methyl or ethyl. In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Ic), R<sup>6</sup> is ethyl. In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Ic), R<sup>6</sup> is polyethylene glycol.

**[0053]** In some embodiments of a compound of Formula (I) or (Ia), the compound is of Formula (Id), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:

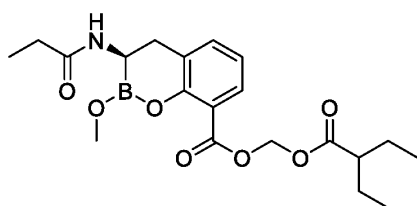


Formula (Id).

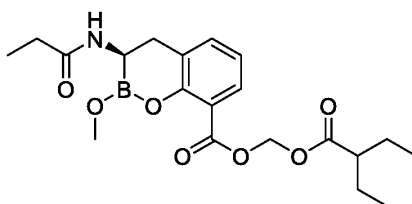
**[0054]** In some embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), or (Id), the compound



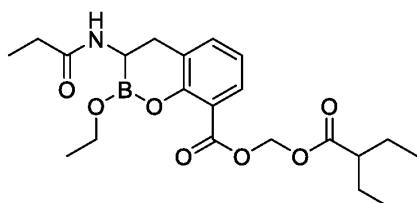
is or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), or (Id), the



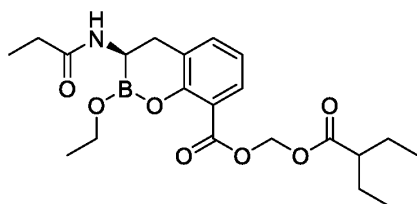
compound is or a pharmaceutically acceptable salt or solvate thereof. In some embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), or (Id), the compound is:



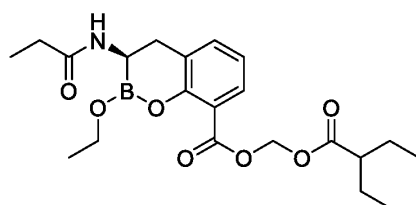
[0055] In some embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), or (Id), the compound



is or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), or (Id), the

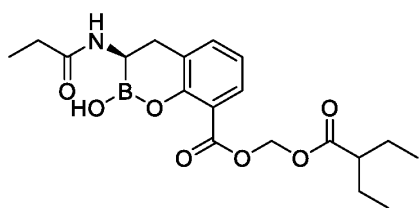


compound is or a pharmaceutically acceptable salt or solvate thereof. In some embodiments of a compound of Formula (I), (Ia), (Ib), (Ic), or (Id), the compound is:

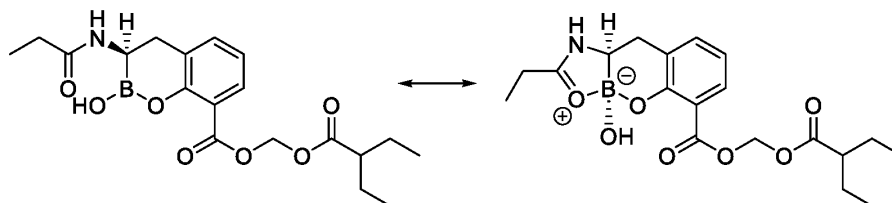


### Compound 1

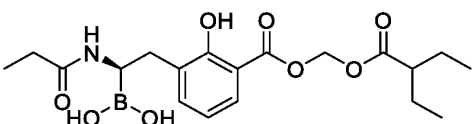
[0056] Also disclosed herein is ((2-ethylbutanoyl)oxy)methyl (R)-2-hydroxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate:



. In some embodiments, ((2-ethylbutanoyl)oxy)methyl (R)-2-hydroxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate is also referred to as Compound 1. In some embodiments, Compound 1 exists in equilibrium as shown below:

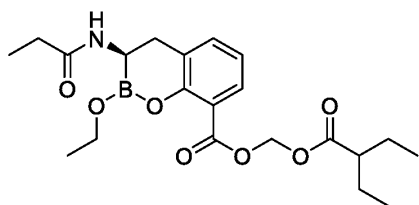


. In some embodiments, Compound 1 exists in an equilibrium between the “closed” cyclic form (as shown

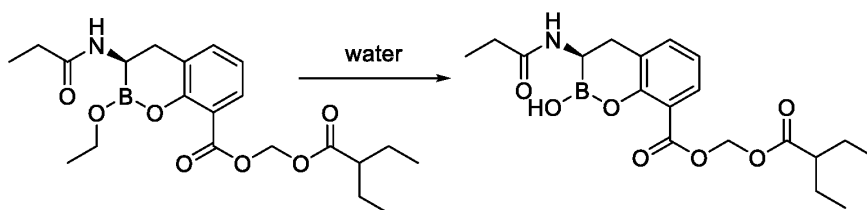
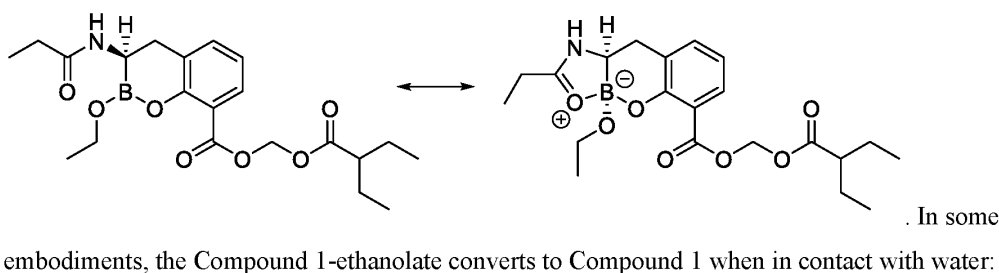
above) and the “open” acyclic form:  ((R)-(2-(3-(((2-ethylbutanoyl)oxy)methoxy)carbonyl)-2-hydroxyphenyl)-1-propionamidoethyl)boronic acid). In some embodiments, Compound 1 associates into intramolecular dimers, trimers, and any combinations thereof. In some embodiments, Compound 1 is in the form of a pharmaceutically acceptable salt. In some embodiments, Compound 1 is in the form of a pharmaceutically acceptable solvate. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein. In some embodiments, Compound 1 is in the form of a pharmaceutically acceptable salt and solvate.

### Compound 1-ethanolate

[0057] In some embodiments, Compound 1 exists in solid form as a covalently bound solvate. In some embodiments, Compound 1 exists in solid form as a covalently bound ethanolate. In some embodiments, Compound 1 in solid form is ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate:

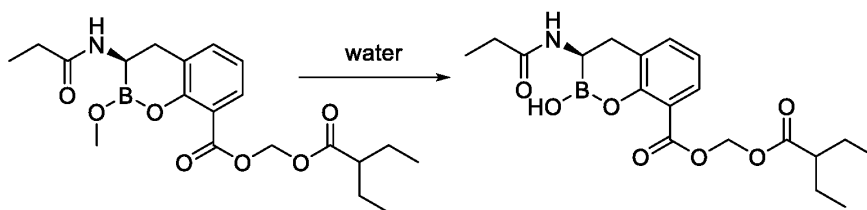
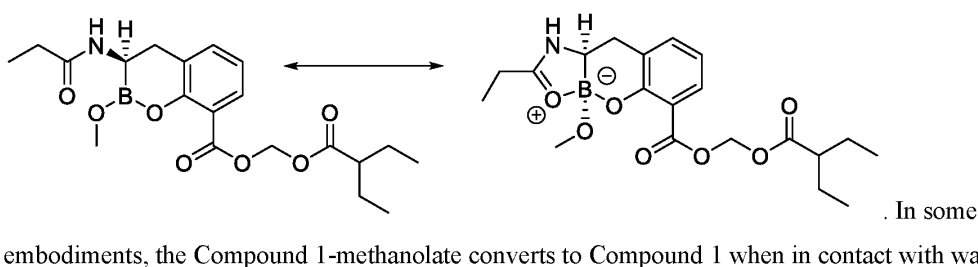
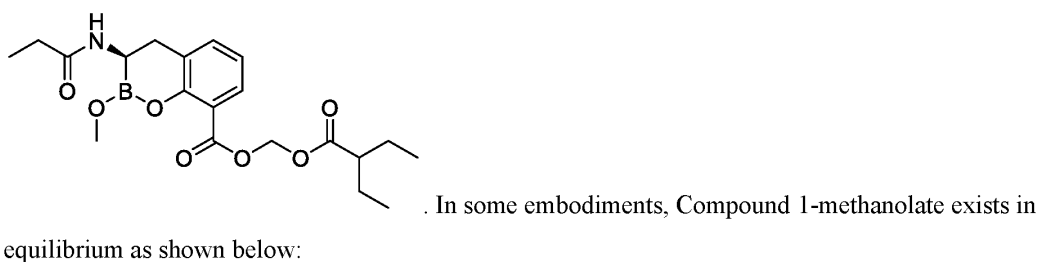


. In some embodiments, Compound 1-ethanolate exists in equilibrium as shown below:



### Compound 1-methanolate

[0058] In some embodiments, Compound 1 exists in solid form as a covalently bound solvate. In some embodiments, Compound 1 exists in solid form as a covalently bound methanolate. In some embodiments, Compound 1 in solid form is ((2-ethylbutanoyl)oxy)methyl (R)-2-methoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate:



**Polymorph Forms**

**[0059]** Disclosed herein are crystalline forms of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate, a pharmaceutically acceptable salt, solvate, or a pharmaceutically acceptable salt and solvate thereof. In some embodiments, disclosed herein is a crystalline forms of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate.

**[0060]** Also described herein are processes for the preparation of the crystalline polymorph Forms A and B.

**Polymorph Form A**

**[0061]** The term “polymorph Form A” or “Form A” refers to a crystalline form of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate that exhibits an X-ray powder diffraction pattern substantially the same as that shown in FIG. 4 and/or a DSC thermogram substantially the same as that shown in FIG. 6. In some embodiments, a polymorph of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate is characterized by the major peaks of FIG. 4. In some embodiments, the major peaks are the peaks of at least 20%, at least 15% or at least 10% of maximum intensity in the XRPD pattern of FIG. 4.

**[0062]** In one embodiment, ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate polymorph Form A exhibits an X-ray powder diffraction pattern characterized by the diffraction pattern summarized in Table 1. In some embodiments, the polymorph Form A of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate comprises at least 3 peaks of ( $\pm 0.1^\circ 2\theta$ ) of Table 1. In certain embodiments, the polymorph Form A of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate comprises at least 4 peaks of ( $\pm 0.1^\circ 2\theta$ ) of Table 1, at least 5 peaks of ( $\pm 0.1^\circ 2\theta$ ) of Table 1, at least 6 peaks of ( $\pm 0.1^\circ 2\theta$ ) of Table 1, at least 7 peaks of ( $\pm 0.1^\circ 2\theta$ ) of Table 1, at least 8 peaks of ( $\pm 0.1^\circ 2\theta$ ) of Table 1, or at least 9 peaks of ( $\pm 0.1^\circ 2\theta$ ) of Table 1.

**[0063]** Polymorph form A crystallizes as needles (FIG. 14A and FIG. 14B) and is thermodynamically stable. In some embodiments, polymorph Form A is more thermodynamically stable than polymorph Form B. In some embodiments, polymorph Form A is less dense than polymorph Form B. In some embodiments, a less dense polymorphic form is preferred for formulation purposes.

**Table 1.** Form A Characteristic XRPD Signals ( $2\theta$ , Cu)

| Angle 2-Theta $^\circ$ | Intensity, normalized | d-value, Ångstrom |
|------------------------|-----------------------|-------------------|
| 3.95                   | 2.7                   | 22.3567           |
| 5.14                   | 100.0                 | 17.1938           |
| 6.11                   | 71.8                  | 14.4653           |

| Angle 2-Theta ° | Intensity, normalized | d-value, Ångstrom |
|-----------------|-----------------------|-------------------|
| 6.81            | 14.9                  | 12.9761           |
| 9.00            | 4.3                   | 9.8237            |
| 9.58            | 5.0                   | 9.2208            |
| 9.89            | 17.4                  | 8.9401            |
| 12.23           | 10.9                  | 7.2318            |
| 12.35           | 13.8                  | 7.1636            |
| 12.66           | 28.7                  | 6.9892            |
| 13.62           | 8.8                   | 6.4982            |
| 14.29           | 11.4                  | 6.1922            |
| 15.52           | 13.8                  | 5.7067            |
| 15.78           | 63.0                  | 5.6111            |
| 16.02           | 16.7                  | 5.5281            |
| 16.33           | 8.9                   | 5.4233            |
| 16.51           | 4.8                   | 5.3641            |
| 17.14           | 19.4                  | 5.1686            |
| 17.87           | 12.3                  | 4.9588            |
| 18.10           | 6.5                   | 4.8967            |
| 19.34           | 16.0                  | 4.5865            |
| 19.84           | 7.2                   | 4.4706            |
| 20.59           | 33.8                  | 4.3105            |
| 21.19           | 10.8                  | 4.1890            |
| 21.91           | 18.0                  | 4.0542            |
| 22.14           | 9.3                   | 4.0127            |
| 22.52           | 10.6                  | 3.9458            |

**[0064]** In certain embodiments, the polymorph Form A of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate comprises characteristic peaks at about  $5.1^{\circ} \pm 0.1^{\circ} 2\theta$ , about  $6.1^{\circ} \pm 0.1^{\circ} 2\theta$ , and about  $15.8^{\circ} \pm 0.1^{\circ} 2\theta$ .

**[0065]** In certain embodiments, the polymorph Form A of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate further comprises characteristic peaks at about  $12.7^{\circ} \pm 0.1^{\circ} 2\theta$ , about  $17.1^{\circ} \pm 0.1^{\circ} 2\theta$ , and about  $20.6^{\circ} \pm 0.1^{\circ} 2\theta$ .

**[0066]** In certain embodiments, the polymorph Form A of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate comprises characteristic peaks at about  $6.1^{\circ} \pm 0.1^{\circ} 2\theta$ , about  $9.9^{\circ} \pm 0.1^{\circ} 2\theta$ , and about  $16.0^{\circ} \pm 0.1^{\circ} 2\theta$ .

[0067] In certain embodiments, the polymorph Form A of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate further comprises characteristic peaks at about  $19.3 \pm 0.1^\circ 2\theta$ , about  $6.8 \pm 0.1^\circ 2\theta$ , and about  $17.9 \pm 0.1^\circ 2\theta$ .

[0068] In certain embodiments, the polymorph Form A of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate further comprises characteristic peaks at about  $14.3 \pm 0.1^\circ 2\theta$  and about  $21.2 \pm 0.1^\circ 2\theta$ .

[0069] In certain embodiments, the polymorph Form A of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate has a broad endotherm having an onset at about  $112.8^\circ\text{C}$ .

### *Polymorph Form B*

[0070] The term “polymorph Form B” or “Form B” or refers to a crystalline form of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate that exhibits an X-ray powder diffraction pattern substantially the same as that shown in FIG. 10, and/or a DSC thermogram substantially the same as that shown in FIG. 11.

[0071] In one embodiment, ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate polymorph Form B exhibits an X-ray powder diffraction pattern characterized by the diffraction pattern summarized in Table 2. In some embodiments, the polymorph Form B of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate comprises at least 3 peaks of ( $\pm 0.1^\circ 2\theta$ ) of Table 2. In certain embodiments, the polymorph Form B of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate comprises at least 4 peaks of ( $\pm 0.1^\circ 2\theta$ ) of Table 2, at least 5 peaks of ( $\pm 0.1^\circ 2\theta$ ) of Table 2, at least 6 peaks of ( $\pm 0.1^\circ 2\theta$ ) of Table 2, at least 7 peaks of ( $\pm 0.1^\circ 2\theta$ ) of Table 2, at least 8 peaks of ( $\pm 0.1^\circ 2\theta$ ) of Table 2, or at least 9 peaks of ( $\pm 0.1^\circ 2\theta$ ) of Table 2.

[0072] Polymorph Form B crystallizes as large plates (FIG. 15A and FIG. 15B). In some embodiments, large plates are easier to handle and purify.

**Table 2.** Form B Characteristic XRPD Signals ( $2\theta$ , Cu K $\alpha$ 1)

| Angle 2-Theta $^\circ$ | Intensity, normalized | d-value, Ångstrom |
|------------------------|-----------------------|-------------------|
| 5.10                   | 100.0                 | 17.3010           |
| 8.80                   | 10.5                  | 10.0414           |
| 9.29                   | 20.8                  | 9.5172            |
| 12.02                  | 11.1                  | 7.3557            |
| 12.35                  | 13.6                  | 7.1589            |
| 12.86                  | 21.6                  | 6.8783            |
| 14.60                  | 10.5                  | 6.0637            |
| 15.06                  | 5.4                   | 5.8780            |

| Angle 2-Theta ° | Intensity, normalized | d-value, Ångstrom |
|-----------------|-----------------------|-------------------|
| 15.34           | 7.0                   | 5.7702            |
| 15.56           | 39.5                  | 5.6923            |
| 16.76           | 4.1                   | 5.2858            |
| 17.33           | 15.0                  | 5.1121            |
| 18.48           | 5.2                   | 4.7966            |
| 18.64           | 7.4                   | 4.7565            |
| 19.92           | 12.2                  | 4.4536            |
| 20.25           | 3.2                   | 4.3819            |
| 20.50           | 21.4                  | 4.3280            |
| 20.92           | 4.0                   | 4.2429            |
| 21.54           | 17.4                  | 4.1222            |
| 21.97           | 5.8                   | 4.0429            |
| 22.31           | 7.9                   | 3.9810            |
| 23.49           | 5.0                   | 3.7846            |
| 24.60           | 6.5                   | 3.6166            |
| 27.84           | 4.5                   | 3.2016            |

**[0073]** In certain embodiments, the polymorph Form B of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate comprises characteristic peaks at about  $5.1^{\circ} \pm 0.1^{\circ} 2\theta$ , about  $12.9^{\circ} \pm 0.1^{\circ} 2\theta$ , and about  $15.6^{\circ} \pm 0.1^{\circ} 2\theta$ .

**[0074]** In certain embodiments, the polymorph Form B of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate further comprises characteristic peaks at about  $9.3^{\circ} \pm 0.1^{\circ} 2\theta$ , about  $20.5^{\circ} \pm 0.1^{\circ} 2\theta$ , and about  $21.5^{\circ} \pm 0.1^{\circ} 2\theta$ .

**[0075]** In certain embodiments, the polymorph Form B of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate comprises characteristic peaks at about  $9.3^{\circ} \pm 0.1^{\circ} 2\theta$ , about  $12.9^{\circ} \pm 0.1^{\circ} 2\theta$ , and about  $21.5^{\circ} \pm 0.1^{\circ} 2\theta$ .

**[0076]** In certain embodiments, the polymorph Form B of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate further comprises characteristic peaks at about  $8.8^{\circ} \pm 0.1^{\circ} 2\theta$ , about  $14.6^{\circ} \pm 0.1^{\circ} 2\theta$ , and about  $17.3^{\circ} \pm 0.1^{\circ} 2\theta$ .

### Methods of Treatment

**[0077]** The present disclosure also provides methods for inhibiting bacterial growth, by, e.g., reducing bacterial resistance to a  $\beta$ -lactam antibiotic, such methods comprising contacting a bacterial cell culture, or a bacterially infected cell culture, tissue, or organism, with Compound 1-ethanolate, a pharmaceutically acceptable salt, a solvate, or a pharmaceutically acceptable salt and solvate thereof. In some embodiments, the bacteria to be inhibited by administration of Compound 1-ethanolate, a

pharmaceutically acceptable salt, a solvate thereof, or a pharmaceutically acceptable salt and solvate thereof are bacteria that are resistant to beta-lactam antibiotics. The term “resistant” is well-understood by those of ordinary skill in the art (see, e.g. Payne et al., *Antimicrobial Agents and Chemotherapy* 38 767-772 (1994), Hanaki et al., *Antimicrobial Agents and Chemotherapy* 30 1120-1126 (1995)).

**[0078]** These methods are useful for inhibiting bacterial growth in a variety of contexts. In certain embodiments, Compound 1-ethanolate, a pharmaceutically acceptable salt, a solvate, or a pharmaceutically acceptable salt and solvate thereof is administered to an experimental cell culture *in vitro* to prevent the growth of beta-lactam resistant bacteria. In certain other embodiments, Compound 1-ethanolate, a pharmaceutically acceptable salt, a solvate, or a pharmaceutically acceptable salt and solvate thereof is administered to a mammal, including a human to prevent the growth of beta-lactam resistant bacteria *in vivo*. The method according to this embodiment comprises administering a therapeutically effective amount of a beta-lactamase inhibitor for a therapeutically effective period of time to a mammal, including a human. Preferably, the beta-lactamase inhibitor is administered in the form of a pharmaceutical composition as described above. In some embodiments, an antibiotic is co-administered with the beta-lactamase inhibitor. In some embodiments, the antibiotic is a beta-lactam antibiotic. In some embodiments, the beta-lactam antibiotic is ceftibuten, or a salt thereof. In some embodiments, the beta-lactam antibiotic is cefixime, or a salt thereof.

**[0079]** In another aspect provided herein are methods of treating a bacterial infection, which method comprises administering to a subject a pharmaceutical composition comprising Compound 1-ethanolate, a pharmaceutically acceptable salt, a solvate, or a pharmaceutically acceptable salt and solvate thereof, and a pharmaceutically acceptable excipient as described above. In some embodiments, the bacterial infection is an upper or lower respiratory tract infection, a urinary tract infection, an intra-abdominal infection, or a skin infection.

**[0080]** In some embodiments, the infection that is treated or prevented comprises a bacteria that includes *Elizabethkingia meningoseptica*, *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Pseudomonas acidovorans*, *Pseudomonas alcaligenes*, *Pseudomonas putida*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Aeromonas hydrophilia*, *Escherichia coli*, *Citrobacter freundii*, *Salmonella typhimurium*, *Salmonella typhi*, *Salmonella paratyphi*, *Salmonella enteritidis*, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Serratia marcescens*, *Francisella tularensis*, *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia alcalifaciens*, *Providencia rettgeri*, *Providencia stuartii*, *Acinetobacter baumannii*, *Acinetobacter calcoaceticus*, *Acinetobacter haemolyticus*, *Yersinia enterocolitica*, *Yersinia pestis*, *Yersinia pseudotuberculosis*, *Yersinia intermedia*, *Bordetella pertussis*, *Bordetella parapertussis*, *Bordetella bronchiseptica*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Haemophilus haemolyticus*, *Haemophilus parahaemolyticus*, *Haemophilus ducreyi*, *Pasteurella multocida*, *Pasteurella haemolytica*,

*Branhamella catarrhalis*, *Helicobacter pylori*, *Campylobacter fetus*, *Campylobacter jejuni*, *Campylobacter coli*, *Borrelia burgdorferi*, *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Legionella pneumophila*, *Listeria monocytogenes*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Kingella*, *Moraxella*, *Gardnerella vaginalis*, *Bacteroides fragilis*, *Bacteroides distasonis*, *Bacteroides* 3452A homology group, *Bacteroides vulgatus*, *Bacteroides ovalis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides eggerthii*, *Bacteroides splanchnicus*, *Clostridium difficile*, *Mycobacterium tuberculosis*, *Mycobacterium avium*, *Mycobacterium intracellulare*, *Mycobacterium leprae*, *Corynebacterium diphtheriae*, *Corynebacterium ulcerans*, *Streptococcus pneumoniae*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Staphylococcus intermedius*, *Staphylococcus hyicus* subsp. *hyicus*, *Staphylococcus haemolyticus*, *Staphylococcus hominis*, or *Staphylococcus saccharolyticus*.

[0081] In some embodiments, the infection that is treated or prevented comprises a bacteria that includes *Elizabethkingia meningoseptica*, *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Stenotrophomonas maltophilia*, *Escherichia coli*, *Citrobacter freundii*, *Salmonella typhimurium*, *Salmonella typhi*, *Salmonella paratyphi*, *Salmonella enteritidis*, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Serratia marcescens*, *Acinetobacter calcoaceticus*, *Acinetobacter haemolyticus*, *Yersinia enterocolitica*, *Yersinia pestis*, *Yersinia pseudotuberculosis*, *Yersinia intermedia*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Haemophilus haemolyticus*, *Haemophilus parahaemolyticus*, *Helicobacter pylori*, *Campylobacter fetus*, *Campylobacter jejuni*, *Campylobacter coli*, *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Legionella pneumophila*, *Listeria monocytogenes*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Moraxella*, *Bacteroides fragilis*, *Bacteroides vulgatus*, *Bacteroides ovalis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides eggerthii*, or *Bacteroides splanchnicus*.

### Certain Definitions

[0082] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, certain preferred methods, devices, and materials are now described.

[0083] As used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to “an excipient” is a reference to one or more excipients and equivalents thereof known to those skilled in the art, and so forth.

[0084] The term “about” is used to indicate that a value includes the standard level of error for the device or method being employed to determine the value.

[0085] The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and to “and/or.”

[0086] The terms “comprise,” “have” and “include” are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as “comprises,” “comprising,” “has,” “having,” “includes” and “including,” are also open-ended. For example, any method that “comprises,” “has” or “includes” one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

[0087] “Optional” or “optionally” may be taken to mean that the subsequently described structure, event or circumstance may or may not occur, and that the description includes instances where the events occurs and instances where it does not.

[0088] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0089] “Aliphatic chain” refers to a linear chemical moiety that is composed of only carbons and hydrogens. In some embodiments, the aliphatic chain is saturated. In some embodiments, the aliphatic chain is unsaturated. In some embodiments, the unsaturated aliphatic chain contains one unsaturation. In some embodiments, the unsaturated aliphatic chain contains more than one unsaturation. In some embodiments, the unsaturated aliphatic chain contains two unsaturations. In some embodiments, the unsaturated aliphatic chain contains one double bond. In some embodiments, the unsaturated aliphatic chain contains two double bonds.

[0090] “Alkyl” refers to an optionally substituted straight-chain, or optionally substituted branched-chain saturated hydrocarbon monoradical having from one to about ten carbon atoms, or from one to six carbon atoms. Examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl, and hexyl, and longer alkyl groups, such as heptyl, octyl, and the like. Whenever it appears herein, a numerical range such as “C<sub>1</sub>-C<sub>6</sub> alkyl” means that the alkyl group consists of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated. In some embodiments, the alkyl is a C<sub>1</sub>-C<sub>10</sub> alkyl, a C<sub>1</sub>-C<sub>9</sub> alkyl, a C<sub>1</sub>-C<sub>8</sub> alkyl, a C<sub>1</sub>-C<sub>7</sub> alkyl, a C<sub>1</sub>-C<sub>6</sub> alkyl, a C<sub>1</sub>-C<sub>5</sub> alkyl, a C<sub>1</sub>-C<sub>4</sub> alkyl, a C<sub>1</sub>-C<sub>3</sub> alkyl, a C<sub>1</sub>-C<sub>2</sub> alkyl, or a C<sub>1</sub> alkyl. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkyl is optionally substituted with oxo, halogen, -CN, -CF<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -

NO<sub>2</sub>. In some embodiments, the alkyl is optionally substituted with oxo, halogen, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the alkyl is optionally substituted with halogen.

**[0091]** “Alkenyl” refers to an optionally substituted straight-chain, or optionally substituted branched-chain hydrocarbon monoradical having one or more carbon-carbon double-bonds and having from two to about ten carbon atoms, more preferably two to about six carbon atoms. The group may be in either the *cis* or *trans* conformation about the double bond(s), and should be understood to include both isomers. Examples include, but are not limited to, ethenyl (-CH=CH<sub>2</sub>), 1-propenyl (-CH<sub>2</sub>CH=CH<sub>2</sub>), isopropenyl [-C(CH<sub>3</sub>)=CH<sub>2</sub>], butenyl, 1,3-butadienyl, and the like. Whenever it appears herein, a numerical range such as “C<sub>2</sub>-C<sub>6</sub> alkenyl” means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkenyl” where no numerical range is designated. In some embodiments, the alkenyl is a C<sub>2</sub>-C<sub>10</sub> alkenyl, a C<sub>2</sub>-C<sub>9</sub> alkenyl, a C<sub>2</sub>-C<sub>8</sub> alkenyl, a C<sub>2</sub>-C<sub>7</sub> alkenyl, a C<sub>2</sub>-C<sub>6</sub> alkenyl, a C<sub>2</sub>-C<sub>5</sub> alkenyl, a C<sub>2</sub>-C<sub>4</sub> alkenyl, a C<sub>2</sub>-C<sub>3</sub> alkenyl, or a C<sub>2</sub> alkenyl. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkenyl is optionally substituted with oxo, halogen, -CN, -CF<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, an alkenyl is optionally substituted with oxo, halogen, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the alkenyl is optionally substituted with halogen.

**[0092]** “Alkynyl” refers to an optionally substituted straight-chain or optionally substituted branched-chain hydrocarbon monoradical having one or more carbon-carbon triple-bonds and having from two to about ten carbon atoms, more preferably from two to about six carbon atoms. Examples include, but are not limited to, ethynyl, 2-propynyl, 2-butyne, 1,3-butadiynyl, and the like. Whenever it appears herein, a numerical range such as “C<sub>2</sub>-C<sub>6</sub> alkynyl” means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkynyl” where no numerical range is designated. In some embodiments, the alkynyl is a C<sub>2</sub>-C<sub>10</sub> alkynyl, a C<sub>2</sub>-C<sub>9</sub> alkynyl, a C<sub>2</sub>-C<sub>8</sub> alkynyl, a C<sub>2</sub>-C<sub>7</sub> alkynyl, a C<sub>2</sub>-C<sub>6</sub> alkynyl, a C<sub>2</sub>-C<sub>5</sub> alkynyl, a C<sub>2</sub>-C<sub>4</sub> alkynyl, a C<sub>2</sub>-C<sub>3</sub> alkynyl, or a C<sub>2</sub> alkynyl. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkynyl is optionally substituted with oxo, halogen, -CN, -CF<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, an alkynyl is optionally substituted with oxo, halogen, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the alkynyl is optionally substituted with halogen.

**[0093]** “Alkylene” refers to a straight or branched divalent hydrocarbon chain. Unless stated otherwise specifically in the specification, an alkylene group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl,

heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkylene is optionally substituted with oxo, halogen, -CN, -CF<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, an alkylene is optionally substituted with oxo, halogen, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the alkylene is optionally substituted with halogen.

**[0094]** “Alkoxy” refers to a radical of the formula -OR<sub>a</sub> where R<sub>a</sub> is an alkyl radical as defined. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an alkoxy is optionally substituted with oxo, halogen, -CN, -CF<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, an alkoxy is optionally substituted with oxo, halogen, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the alkoxy is optionally substituted with halogen.

**[0095]** “Aminoalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more amines. In some embodiments, the alkyl is substituted with one amine. In some embodiments, the alkyl is substituted with one, two, or three amines. Hydroxyalkyl include, for example, aminomethyl, aminoethyl, aminopropyl, aminobutyl, or aminopentyl. In some embodiments, the hydroxyalkyl is aminomethyl.

**[0096]** “Aryl” refers to a radical derived from a hydrocarbon ring system comprising hydrogen, 6 to 30 carbon atoms, and at least one aromatic ring. The aryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the aryl is bonded through an aromatic ring atom) or bridged ring systems. In some embodiments, the aryl is a 6- to 10-membered aryl. In some embodiments, the aryl is a 6-membered aryl. Aryl radicals include, but are not limited to, aryl radicals derived from the hydrocarbon ring systems of anthrylene, naphthylene, phenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, as-indacene, s-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. In some embodiments, the aryl is phenyl. Unless stated otherwise specifically in the specification, an aryl may be optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, an aryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, an aryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the aryl is optionally substituted with halogen.

**[0097]** “Cycloalkyl” refers to a stable, partially or fully saturated, monocyclic or polycyclic carbocyclic ring, which may include fused (when fused with an aryl or a heteroaryl ring, the cycloalkyl is bonded through a non-aromatic ring atom), bridged, or spiro ring systems. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms (C<sub>3</sub>-C<sub>15</sub> cycloalkyl), from three to ten carbon atoms (C<sub>3</sub>-C<sub>10</sub> cycloalkyl), from three to eight carbon atoms (C<sub>3</sub>-C<sub>8</sub> cycloalkyl), from three to six carbon atoms (C<sub>3</sub>-C<sub>6</sub> cycloalkyl), from three

to five carbon atoms (C<sub>3</sub>-C<sub>5</sub> cycloalkyl), or three to four carbon atoms (C<sub>3</sub>-C<sub>4</sub> cycloalkyl). In some embodiments, the cycloalkyl is a 3- to 6-membered cycloalkyl. In some embodiments, the cycloalkyl is a 5- to 6-membered cycloalkyl. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls or carbocycles include, for example, adamantyl, norbornyl, decalyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Partially saturated cycloalkyls include, for example, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless stated otherwise specifically in the specification, a cycloalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the cycloalkyl is optionally substituted with halogen.

**[0098]** “Deuteroalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more deuteriums. In some embodiments, the alkyl is substituted with one deuterium. In some embodiments, the alkyl is substituted with one, two, or three deuteriums. In some embodiments, the alkyl is substituted with one, two, three, four, five, or six deuteriums. Deuteroalkyl include, for example, CD<sub>3</sub>, CH<sub>2</sub>D, CHD<sub>2</sub>, CH<sub>2</sub>CD<sub>3</sub>, CD<sub>2</sub>CD<sub>3</sub>, CHDCD<sub>3</sub>, CH<sub>2</sub>CH<sub>2</sub>D, or CH<sub>2</sub>CHD<sub>2</sub>. In some embodiments, the deuteroalkyl is CD<sub>3</sub>.

**[0099]** “Haloalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more halogens. In some embodiments, the alkyl is substituted with one, two, or three halogens. In some embodiments, the alkyl is substituted with one, two, three, four, five, or six halogens. Haloalkyl include, for example, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. In some embodiments, the haloalkyl is trifluoromethyl.

**[0100]** “Halo” or “halogen” refers to bromo, chloro, fluoro, or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

**[0101]** “Heteroalkyl” refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, e.g., oxygen, nitrogen (e.g., -NH-, -N(alkyl)-), sulfur, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C<sub>1</sub>-C<sub>6</sub> heteroalkyl wherein the heteroalkyl is comprised of 1 to 6 carbon atoms and one or more atoms other than carbon, e.g., oxygen, nitrogen (e.g., -NH-, -N(alkyl)-), sulfur, or combinations thereof wherein the heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. Examples of such heteroalkyl are, for example, -CH<sub>2</sub>OCH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, or -CH(CH<sub>3</sub>)OCH<sub>3</sub>. Unless stated otherwise

specifically in the specification, a heteroalkyl is optionally substituted for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the heteroalkyl is optionally substituted with halogen.

**[0102]** “Hydroxyalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more hydroxyls. In some embodiments, the alkyl is substituted with one hydroxyl. In some embodiments, the alkyl is substituted with one, two, or three hydroxyls. Hydroxyalkyl include, for example, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, or hydroxypentyl. In some embodiments, the hydroxyalkyl is hydroxymethyl.

**[0103]** “Heterocycloalkyl” refers to a stable 3- to 24-membered partially or fully saturated ring radical comprising 2 to 23 carbon atoms and from one to 8 heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, and sulfur. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non-aromatic ring atom) or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heterocycloalkyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Representative heterocycloalkyls include, but are not limited to, heterocycloalkyls having from two to fifteen carbon atoms (C<sub>2</sub>-C<sub>15</sub> heterocycloalkyl), from two to ten carbon atoms (C<sub>2</sub>-C<sub>10</sub> heterocycloalkyl), from two to eight carbon atoms (C<sub>2</sub>-C<sub>8</sub> heterocycloalkyl), from two to six carbon atoms (C<sub>2</sub>-C<sub>6</sub> heterocycloalkyl), from two to five carbon atoms (C<sub>2</sub>-C<sub>5</sub> heterocycloalkyl), or two to four carbon atoms (C<sub>2</sub>-C<sub>4</sub> heterocycloalkyl). In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkyl. In some embodiments, the cycloalkyl is a 5- to 6-membered heterocycloalkyl. Examples of such heterocycloalkyl radicals include, but are not limited to, aziridinyl, azetidiny, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazoliny, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, 1,3-dihydroisobenzofuran-1-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl, methyl-2-oxo-1,3-dioxol-4-yl, and 2-oxo-1,3-dioxol-4-yl. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to, the monosaccharides, the disaccharides, and the oligosaccharides. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring). Unless stated otherwise specifically in the specification, a heterocycloalkyl

is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heterocycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, a heterocycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the heterocycloalkyl is optionally substituted with halogen.

**[0104]** “Heteroaryl” refers to a 5- to 14-membered ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, and sulfur, and at least one aromatic ring. The heteroaryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the heteroaryl is bonded through an aromatic ring atom) or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heteroaryl is a 5- to 10-membered heteroaryl. In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolyl, isoindolyl, isoquinolyl, indolizyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e., thienyl). Unless stated otherwise specifically in the specification, a heteroaryl is optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF<sub>3</sub>, -OH, -OMe, -NH<sub>2</sub>, or -NO<sub>2</sub>. In some embodiments, a heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF<sub>3</sub>, -OH, or -OMe. In some embodiments, the heteroaryl is optionally substituted with halogen.

**[0105]** As used herein, the term “therapeutic” means an agent utilized to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient.

**[0106]** “Administering” when used in conjunction with a therapeutic means to administer a therapeutic systemically or locally, as directly into or onto a target tissue, or to administer a therapeutic to a patient whereby the therapeutic positively impacts the tissue to which it is targeted.

“Administering” a pharmaceutical composition may be accomplished by injection, topical administration, and oral administration or by other methods alone or in combination with other known techniques.

**[0107]** The term “animal” as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. As used herein, the terms “patient,” “subject” and “individual” are intended to include living organisms in which certain conditions as described herein can occur. Examples include humans, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and transgenic species thereof. In a preferred embodiment, the patient is a primate. In certain embodiments, the primate or subject is a human. In certain instances, the human is an adult. In certain instances, the human is child. In further instances, the human is 12 years of age or younger. In certain instances, the human is elderly. In other instances, the human is 60 years of age or older. Other examples of subjects include experimental animals such as mice, rats, dogs, cats, goats, sheep, pigs, and cows.

**[0108]** By “pharmaceutically acceptable,” it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

**[0109]** The term “pharmaceutical composition” means a composition comprising at least one active ingredient, such as Compound 1-ethanolate, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

**[0110]** A “therapeutically effective amount” or “effective amount” as used herein refers to the amount of active compound or pharmaceutical agent that elicits a biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease, (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

**[0111]** The terms “treat,” “treated,” “treatment,” or “treating” as used herein refers to both therapeutic treatment in some embodiments and prophylactic or preventative measures in other embodiments, wherein the object is to prevent or slow (lessen) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results. For the purposes described

herein, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether detectable or undetectable, or enhancement or improvement of the condition, disorder or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. A prophylactic benefit of treatment includes prevention of a condition, retarding the progress of a condition, stabilization of a condition, or decreasing the likelihood of occurrence of a condition. As used herein, “treat,” “treated,” “treatment,” or “treating” includes prophylaxis in some embodiments.

[0112] The term “substantially the same as” as used herein, refers to a powder x-ray diffraction pattern or differential scanning calorimetry pattern that is non-identical to those depicted herein, but that falls within the limits of experimental error, when considered by one of ordinary skill in the art.

## EXAMPLES

### Analytical Methods

#### *High-resolution Mass Spectrometry (HRMS)*

[0113] High resolution mass spectra from 50 to 3000 Da were collected with a Bruker Maxis-Plus QTOF mass spectrometer using an electrospray ionization source. The instrument was controlled and data analyzed using Bruker Compass v.4.4 software. The mass spectrometer was calibrated immediately prior to analyses and was operated in positive ionization mode using an Electrospray Ionization (ESI) source. Samples were prepared by dilution in absolute ethanol (without denaturants) or HPLC grade water prior to direct infusion into the ion source.

#### *Raman Spectroscopy*

[0114] Raman spectra were acquired on a Bruker MultiRAM with OPUS 7.0 software. The samples were measured using truncated NMR tubes that were filled in a N<sub>2</sub>-filled glovebox at approximately 0% RH. A 300 mW laser power from a Nd:YAG laser (1064 nm excitation wavelength) was used to irradiate the sample. Each spectrum represents 64 co-added scans collected at a spectral resolution of 2 cm<sup>-1</sup>.

#### *FT-IR Spectroscopy (FT-IR)*

[0115] Infrared spectra were acquired using a Nicolet 6700 Fourier transform infrared (FT-IR) spectrophotometer (Thermo Nicolet) equipped with an Ever-Glo mid/far IR source, an extended range potassium bromide (KBr) beamsplitter, and a deuterated triglycine sulfate (DTGS)) detector. Wavelength verification was performed using NIST SRM 1921b (polystyrene). An attenuated total reflectance (ATR) accessory (Thunderdome™, Thermo Spectra-Tech) equipped with a germanium (Ge) crystal was used for data acquisition. Each sample was placed directly on the clean Ge crystal for

analysis. Each spectrum represents 256 co-added scans collected at a spectral resolution of  $4\text{ cm}^{-1}$ . A background data set was acquired with a clean Ge crystal.

#### *X-ray powder diffraction*

[0116] XRPD patterns were collected with two conditions. A PANalytical X'Pert PRO MPD diffractometer using an incident beam of Cu K $\alpha$  radiation produced using a long, fine-focus source and a nickel filter. An elliptically graded multilayer mirror was used to focus Cu K $\alpha$  X-rays through the specimen and onto the detector. Data were collected and analyzed using Data Collector software v. 2.2b. Prior to the analysis, a silicon specimen (NIST SRM 640e) was analyzed to verify the observed position of the Si 111 peak was consistent with the NIST-certified position. A specimen of the sample was sandwiched between 3- $\mu\text{m}$ -thick films and analyzed in transmission geometry. Anti-scatter slits (SS) were used to minimize the background generated by air. Soller slits for the incident and diffracted beams were used to minimize broadening from axial divergence. Diffraction patterns were collected using a scanning position-sensitive detector (X'Celerator) located 240 mm from the sample and Data Collector software v. 2.2b. The data acquisition parameters for each pattern are displayed above the image in the Data section of this report including the divergence slit (DS).

[0117] A second method used a Bruker D8 Advance using Cu K $\alpha$  radiation of 40 kV/40 mA. Data were collected with a LynxEye detector in Bragg-Brentano reflection geometry with a  $0.02^\circ 2\theta$  step size, 37 s step time over  $2.5\text{--}50^\circ 2\theta$  range. The powder samples were measured in 0.05 mm deep silicon single-crystal sample holders covered with a Kapton foil to protect them from moisture. The samples were placed in an inert atmosphere environment ( $\text{N}_2$ -filled glovebox) but no other special treatment was used in preparing the samples other than the application of slight pressure to obtain a flat surface. All samples were rotated during the measurement.

#### *Indexing*

[0118] XRPD patterns were indexed using TRIADS3. Indexing and structure refinement are computational studies. Agreement between the allowed peak positions, marked with red bars, and the observed peaks indicates a consistent unit cell determination. Successful indexing of the pattern indicates that the sample is composed primarily of a single crystalline phase. Space groups consistent with the assigned extinction symbol, unit cell parameters, and derived quantities are tabulated below each figure showing tentative indexing solution. To confirm the tentative indexing solution, the molecular packing motifs within the crystallographic unit cells must be determined. No attempts at molecular packing were performed.

#### *Polarized Light Microscopy (PLM)*

[0119] Polarized light microscopy was performed using a Leica MZ12.5 or Fisher Scientific Stereomaster stereomicroscope. Samples were observed using 0.8-10x objectives with crossed polarizers.

***Differential scanning calorimetry (DSC) analysis***

[0120] DSC was performed using a TA Instruments 2920 or Q2000 differential scanning calorimeter equipped with a refrigerated cooling system (RCS). Temperature calibration was performed using NIST-traceable indium metal. The sample was placed into an aluminum DSC pan, covered with a lid, and the weight was accurately recorded. A weighed aluminum pan configured as the sample pan was placed on the reference side of the cell. The data acquisition parameters and pan configuration for each thermogram are captured for each analysis. The method code on the thermogram is an abbreviation for the start and end temperature as well as the heating rate; e.g., -30-250-10 means “from -30 °C to 250 °C, at 10 °C/min”.

***Dynamic vapor sorption (DVS) analysis***

[0121] Moisture sorption/desorption data were collected on a VTI SGA-100 Vapor Sorption Analyzer. NaCl and PVP were used as calibration standards. Samples were not dried prior to analysis. Sorption and desorption data were collected over a range from 5% to 95% RH at 10% RH increments under a nitrogen purge (RH = relative humidity). The equilibrium criterion used for analysis was less than 0.0100% weight change in 5 minutes with a maximum equilibration time of 3 hours. Data were not corrected for the initial moisture content of the samples.

[0122] A second set of DVS experiments were conducted using a stepped method from 0% RH to 60% RH with steps of 10% RH and four hours of equilibration at each humidity value. These data were collected on a Project Messtechnik (now ProUmid) SPS11-100n. The samples were placed on an aluminum holder and allowed to equilibrate at 0% RH before starting the following predefined humidity program: hold for 4 h at 0% RH, increase humidity by a step of 10% RH, hold for 4 h, repeat the above two steps five times until a value of 60% RH has been reached. The samples were then analyzed for crystallinity using the second set of XRPD conditions.

***Hot Stage Microscopy (HSM)***

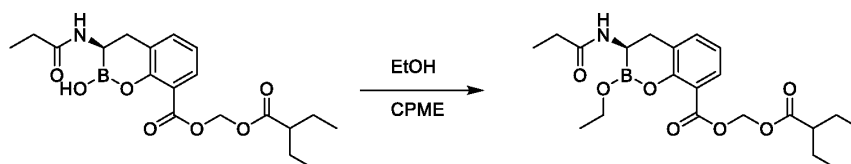
[0123] Hot stage microscopy was performed using a Linkam hot stage (FTIR 600) mounted on a Leica DM LP microscope equipped with a SPOT Insight™ color digital camera. Temperature calibrations were performed using USP melting point standards. Samples were placed on a cover glass, and a second cover glass was placed on top of the sample. As the stage was heated, each sample was visually observed using a 20x objective with crossed polarizers and a first order red compensator. Images were captured using SPOT software (v. 4.5.9).

***Thermogravimetric Analysis (TGA)***

[0124] TGA was performed using a TA Instruments Q5000 IR thermogravimetric analyzer. Temperature calibration was performed using nickel and Alumel™. The sample was placed in an aluminum pan. The sample was hermetically sealed, the lid pierced, then inserted into the TG furnace. The furnace was heated under nitrogen. The data acquisition parameters for each thermogram are displayed in the data image. The method code on the thermogram is an abbreviation for the start and

end temperature as well as the heating rate; e.g., 00-350-10 means “from ambient to 350 °C, at 10 °C/min”.

**Example 1: Preparation and Characterization of ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate (Compound 1-ethanolate), Form A.**



**[0125]** A solution of ((2-ethylbutanoyl)oxy)methyl (R)-2-hydroxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate (Compound 1) in 18 volumes of cyclopentyl methyl ether (CPME) was distilled under vacuum to until the volume was reduced to 7.5 volumes while maintaining a temperature below  $\leq 65$  °C. A Karl Fischer titration was performed to ensure the level of residual water was reduced to a value below 5000 ppm. The solution was diluted to 17 volumes with additional CPME followed by 6 volumes of ethanol. The solution was distilled under vacuum until a volume of  $\sim 7.5$  volumes was achieved. The composition of the solution was examined to ensure that the level of residual water was below 1000 ppm by KF and the ethanol content was between 6 and 11 volume% determined using  $^1\text{H}$  NMR spectroscopy. The temperature was raised to  $55 \pm 5$  °C over 43 min. and methylcyclohexane (22.5 volumes) added over 50 min while maintaining the temperature at  $55 \pm 5$  °C. The temperature was adjusted to  $45 \pm 5$  °C and the mixture seeded with 0.15% by weight ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate seeds Form A. After addition of the seeds solid formation was observed. The slurry was stirred at  $45 \pm 5$  °C for approximately 4 h, then cooled to  $20 \pm 5$  °C over  $\sim 2.5$  h and stirred for an additional 11 h at  $20 \pm 5$  °C. The product was isolated by filtration under a nitrogen. The solid was washed with methylcyclohexane (7 volumes) over approximately a 7 h period. The resulting wet cake was dried at 30 °C under vacuum to constant weight over about 68 h. The above process provided ((2-ethylbutanoyl)oxy)methyl (R)-2-ethoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate, Form A, in 79% with a purity of 99.7 AUC% by UHPLC.

**Elemental Analysis**

**[0126]** Elemental analysis of Compound 1-ethanolate Form A was conducted (Intertek USA, Inc. QTI Whitehouse Station, NJ, USA). Carbon, hydrogen and nitrogen were determined by an elemental analyzer (Perkin-Elmer 2400 Elemental Analyzer) and the data are presented in Table 3.

Table 3. Elemental Analysis of Compound 1-ethanolate Form A

| Element  | % Theoretical | % Observed |
|----------|---------------|------------|
| Boron    | 2.65          | 2.86       |
| Carbon   | 60.16         | 59.62      |
| Hydrogen | 7.21          | 7.20       |
| Nitrogen | 3.34          | 3.31       |

*Mass Spectrometry*

[0127] The mass spectrum of Compound 1-ethanolate Form A was obtained using a Waters Q-ToF (quadrupole-time of flight hybrid) micromass spectrometer operating in Electrospray Ionization (ESI) positive ion polarity mode. The sample was prepared at a concentration of approximately 2 µg/mL in absolute ethanol, and infused directly into the mass spectrometer source and the tuning parameters were optimized to the compound.

[0128] The mass spectrum included peaks with  $m/z$  442.21 for the  $[M+Na]^+$ , and  $m/z$  861.43 for the  $[2M+Na]^+$  peak, in agreement with the monoisotopic mass of the proposed molecular formula of  $C_{21}H_{30}BNO_7$ . The molecular mass of Compound 1-ethanolate Form A is 419.28 Da and the exact mass is 419.21 Da.

*Nuclear Magnetic Resonance (NMR) Spectroscopy*

[0129] Compound 1-ethanolate Form A was dissolved in 99.8% dichloromethane- $d_2$  ( $CD_2Cl_2$ , 0.8 mL) containing 0.05% (v/v) tetramethylsilane (TMS), as the solvent. To minimize moisture exposure, the sample was prepared under a dry  $N_2$  environment. All NMR data were collected at 300K using a Bruker-Biospin 5 mm gradient broadband probe on a Bruker Biospin AVANCE 500 MHz NMR spectrometer. The 1D proton and carbon-13 spectra were acquired at 500 MHz and 125 MHz, respectively. The spectra were referenced using the tetramethylsilane resonance and set equal to 0.0 ppm for  $^1H$  and  $^{13}C$ .

[0130] The 1D proton spectrum (FIG. 1A) showed the expected chemical shifts, multiplicities and integrations that are consistent with the structure of Compound 1-ethanolate. However, due to presence of residual water in either the  $CD_2Cl_2$  solvent and/or the Compound 1-ethanolate Form A sample, and/or possibly absorption of moisture from the environment, the products of Compound 1-ethanolate Form A hydrolysis, i.e., ((2-ethylbutanoyl)oxy)methyl (*R*)-2-hydroxy-3-propionamido-3,4-dihydro-2*H*-benzo[*e*][1,2]oxaborinine-8-carboxylate and free (unbound) ethanol, were also observed as minor resonances. The observed chemical shifts from the 1D carbon-13 spectrum (FIG. 1B) were consistent with the described chemical structure of Compound 1-ethanolate. Duplicate  $^1H$  and  $^{13}C$  resonances were observed (due to the presence of amide bond rotamers).

Chemical structure of compound 10, showing the numbering of atoms (1-19) used for NMR assignment. The structure is a 1,3-bis(4-oxo-4-phenylbut-1-en-1-yl)-4-phenyl-1,3-dioxane derivative.

| Position No. | Proton Shift <sup>#</sup> (ppm) | Integration    | Proton Multiplicity ( <i>J</i> in Hz) | Carbon Shift <sup>#</sup> (ppm)                                 |
|--------------|---------------------------------|----------------|---------------------------------------|-----------------------------------------------------------------|
| 1            | NA                              | NA             | NA                                    | 159.2, 158.3                                                    |
| 2            | NA                              | NA             | NA                                    | 119.7 <sup>‡</sup> , 118.8 <sup>‡</sup>                         |
| 3            | 7.58                            | 1              | m                                     | 129.6                                                           |
|              | 7.56                            |                | m                                     | 130.0                                                           |
|              | 7.54                            |                | m                                     | 129.8                                                           |
| 4            | 6.73                            | 1              | m                                     | 119.3 <sup>‡</sup> , 119.2 <sup>‡</sup> ,<br>119.1 <sup>‡</sup> |
| 5            | 7.11                            | 1              | bdt ( <i>J</i> = 7.2) <sup>n</sup>    | 134.6, 134.5, 134.4                                             |
|              | 7.07                            |                | bdt ( <i>J</i> = 7.2) <sup>n</sup>    |                                                                 |
| 6            | NA                              | NA             | NA                                    | 128.9, 128.3                                                    |
| 7            | 2.98                            | 1              | dd ( <i>J</i> = 15.4, 4.3)            | 32.9                                                            |
|              | 2.89                            |                | dd ( <i>J</i> = 15.5, 4.5)            |                                                                 |
|              | 2.75                            | 1              | dd ( <i>J</i> = 15.6, 2.1)            |                                                                 |
| 8            | 3.43                            | 0.25           | bs                                    | 46.2, 45.0                                                      |
|              | 3.13                            | 0.05           | bs                                    |                                                                 |
|              | 3.08                            | 0.70           | bs                                    |                                                                 |
| 9            | NA                              | NA             | NA                                    | 165.2, 165.1, 164.6                                             |
| 10           | NA                              | NA             | NA                                    | 181.6, 181.5, 181.1                                             |
| 11           | 2.24                            | 3 <sup>*</sup> | m                                     | 24.4, 24.3                                                      |
| 12           | 0.92                            | 9 <sup>‡</sup> | m                                     | 9.6, 9.5                                                        |
| 13           | 5.94                            | 1.76           | m                                     | 79.6, 79.5, 79.3                                                |
|              | 5.81                            | 0.27           | d ( <i>J</i> = 5.6)                   |                                                                 |
| 14           | NA                              | NA             | NA                                    | 175.5, 175.2                                                    |
| 15           | 2.26                            | 3 <sup>*</sup> | m                                     | 49.0                                                            |
| 16           | 1.63                            | 4.1            | m                                     | 25.2, 25.1                                                      |
|              | 1.54                            |                | m                                     |                                                                 |
| 17           | 0.89                            | 9 <sup>‡</sup> | m                                     | 11.8                                                            |

|                              |            |                  |                     |      |
|------------------------------|------------|------------------|---------------------|------|
| 18                           | 3.87       | 0.7              | m                   | 57.6 |
|                              | 3.79       | 0.7              | m                   | 57.6 |
| 19                           | 1.20       | 2.5 <sup>Δ</sup> | t ( <i>J</i> = 7.0) | 18.2 |
| 8-NH-10                      | 8.47       | 0.04             | bs                  | NA   |
|                              | 8.25, 8.18 | 0.94             | bs                  | NA   |
| CH <sub>2</sub> of Free EtOH | 3.66       | 0.3              | q ( <i>J</i> = 7.0) | 58.6 |
| CH <sub>3</sub> of Free EtOH | 1.19       | 2.5 <sup>Δ</sup> | t ( <i>J</i> = 6.9) | 18.7 |

bdt = broad doublet of triplets, bs = broad singlet, d = doublet, dd = doublet of doublets, m = multiplet, t = triplet, ppm = parts per million.

<sup>#</sup>The splitting of several <sup>1</sup>H and <sup>13</sup>C resonances is most likely due to the presence of rotamers and/or hydrolysis product. NA = Not Applicable. <sup>¥</sup>Assignments can be interchanged. <sup>^</sup>Pair of broad triplets (not resolved completely). <sup>\*</sup>H11 and H15 overlap (total of 3 protons). <sup>†</sup>H12 and H17 overlap (total of 9 protons). <sup>Δ</sup>H19 overlaps with CH<sub>3</sub> peak of free ethanol.

### *Infrared Spectroscopy*

[0131] The Fourier Transformed-Infrared absorption (FT-IR) spectrum of Compound 1-ethanolate Form A was obtained using Attenuated Total Reflectance (ATR) on a Thermo-Nicolet Avatar 370 spectrophotometer using the neat material (See FIG. 2). The FT-IR spectrum band assignments are provided in Table 5. The results are in agreement with the chemical structure of Compound 1-ethanolate.

**Table 5. Characteristic infrared absorption bands (wavenumber) and the corresponding assignments for Compound 1-ethanolate Form A.**

| Wavenumber (cm <sup>-1</sup> )           | Assignment                        |
|------------------------------------------|-----------------------------------|
| 3034, 2974, 2928, 2875                   | C-H                               |
| 1746                                     | C=O                               |
| 1617, 1583                               | C=C                               |
| 1537                                     | NH                                |
| 1454                                     | CH <sub>3</sub> , CH <sub>2</sub> |
| 1285, 1242, 1186, 1149, 1113, 1083, 1056 | C-O, C-N                          |
| 759, 691                                 | Aromatic H                        |

### *Raman Spectroscopy*

The FT-IR and Raman spectra for Compound 1 Form A was collected (See FIG. 3). The peaks are shown in the table below:

| Peak | Wavenumber (cm <sup>-1</sup> ) | Peak | Wavenumber (cm <sup>-1</sup> ) | Peak | Wavenumber (cm <sup>-1</sup> ) |
|------|--------------------------------|------|--------------------------------|------|--------------------------------|
| 1    | 3075                           | 11   | 1366                           | 21   | 919                            |
| 2    | 2969                           | 12   | 1346                           | 22   | 896                            |
| 3    | 2936                           | 13   | 1323                           | 23   | 844                            |
| 4    | 2879                           | 14   | 1249                           | 24   | 804                            |
| 5    | 2836                           | 15   | 1171                           | 25   | 753                            |
| 6    | 2745                           | 16   | 1150                           | 26   | 637                            |
| 7    | 1743                           | 17   | 1107                           | 27   | 562                            |
| 8    | 1589                           | 18   | 1048                           | 28   | 386                            |
| 9    | 1457                           | 19   | 1018                           | 29   | 301                            |
| 10   | 1429                           | 20   | 944                            | 30   | 216                            |

### UV-Vis Spectroscopy

[0132] The Ultraviolet Absorbance Spectrum of Compound 1-ethanolate Form A was obtained on a PerkinElmer Lambda 25 UV-Vis spectrophotometer. The sample solution was prepared in methanol at 0.01 mg/mL. The spectrum absorption maxima with extinction coefficients are provided in Table 6.

**Table 6: Ultraviolet absorbance spectrum absorption maxima and extinction coefficient for Compound 1-ethanolate Form A.**

| Solvent                  | Wavelength (nm) | Absorption | Molar Extinction Coefficient<br>(L mol <sup>-1</sup> cm <sup>-1</sup> ) |
|--------------------------|-----------------|------------|-------------------------------------------------------------------------|
| Methanol<br>(0.01 mg/mL) | 208.3           | 0.66       | 27672                                                                   |
|                          | 238.5           | 0.19       | 7966                                                                    |
|                          | 302.3           | 0.10       | 4193                                                                    |

### Example 2. Solubility studies of Compound 1-ethanolate Form A.

[0133] Visual solubility estimates for Compound 1-ethanolate Form A were determined in a variety of solvents and solvent mixtures using an aliquot addition method to aid in experimental design. In general, Compound 1-ethanolate Form A exhibited good solubility in the majority of the tested solvents. Low solubility (<1 mg/mL) was observed in heptane and cyclohexane. Solubility results are provided in Table 7.

**Table 7: Solubility Estimates of Compound 1-ethanolate Form A at Ambient Temperature.**

| Solvent <sup>a,b</sup> | Solubility (mg/mL) <sup>c</sup> |
|------------------------|---------------------------------|
| Acetone                | 34                              |
| ACN                    | >66                             |
| Anisole                | 35                              |

| Solvent <sup>a,b</sup> | Solubility (mg/mL) <sup>c</sup> |
|------------------------|---------------------------------|
| Chloroform             | 36                              |
| Cyclohexane            | <1                              |
| DCM                    | 34                              |
| Diethyl Ether          | 9                               |
| DMF                    | >63                             |
| DMSO                   | >71                             |
| EtOAc                  | >68                             |
| EtOH                   | >68                             |
| Heptane                | <1                              |
| IPA                    | 34                              |
| IPOAc                  | >66                             |
| MEK                    | 37                              |
| MTBE                   | 22                              |
| Nitromethane           | >68                             |
| TFE                    | >66                             |
| THF                    | >64                             |
| Toluene                | 33                              |
| Xylene                 | 17                              |
| Cyclohexane:EtOAc 3:1  | 4                               |
| Heptane:MEK 2:1        | 22                              |
| Cyclohexane:EtOH 90:10 | 17                              |

- a. Solvents were dried over 3Å molecular sieves prior to use, unless otherwise indicated.  
b. Solvent ratios are by volume.  
c. Solubilities are calculated based on the total solvent used to give a solution; actual solubilities may be greater because of the volume of the solvent portions utilized or a slow rate of dissolution. Solubilities are rounded to the nearest mg/mL.

### Example 3. XRPD characterization of Compound 1-ethanolate Form A.

**[0134]** XRPD analysis indicates Compound 1-ethanolate Form A from Example 1 is composed of a crystalline material. FIG. 4 shows the XRPD pattern for Compound 1-ethanolate Form A. FIG. 5 shows the indexing solution for Compound 1-ethanolate Form A with Cu-K $\alpha$  radiation.

**[0135]** The XRPD pattern of Compound 1-ethanolate Form A was successfully indexed, indicating that the sample is composed primarily or exclusively of a single crystalline phase.

| Bravais Type | Primitive Monoclinic |
|--------------|----------------------|
| a [Å]        | 17.377               |
| b [Å]        | 11.945               |
| c [Å]        | 22.629               |

|                                       |                      |
|---------------------------------------|----------------------|
| $\alpha$ [deg]                        | 90                   |
| $\beta$ [deg]                         | 96.51                |
| $\gamma$ [deg]                        | 90                   |
| Volume [ $\text{\AA}^3/\text{cell}$ ] | 4666.7               |
| Chiral Contents?                      | Chiral               |
| Extinction Symbol                     | P 1 2 <sub>1</sub> 1 |
| Space Group(s)                        | P2 <sub>1</sub> (4)  |

**Example 4. Thermal Analysis of Compound 1-ethanolate Form A.**

[0136] Thermal analysis of Compound 1-ethanolate Form A is presented in FIG. 6. The DSC thermogram of Compound 1-ethanolate Form A exhibits a small broad feature coincident with the onset of a single endotherm at 112.8 °C (peak maximum). The single endotherm is attributed to melting based on hot stage microscopy. A weight loss of 1.2% is observed in the TGA between 24.8 and 120 °C.

[0137] Hot stage microscopy of Compound 1-ethanolate Form A was conducted. Upon heating the sample, no changes were observed up to the onset of melting (i.e., 77.3 °C). Melting was completed at 106.5 °C and, upon cooling, no recrystallization of the melted sample was observed.

**Example 5: Dynamic Vapor Sorption (DVS) Analysis of Compound 1-ethanolate Form A.**

[0138] DVS analysis of Compound 1-ethanolate Form A was conducted from 5% relative humidity (RH) to 95% RH and back to 5% RH at 10% RH increments (FIG. 7). With increasing RH, the sample showed ~0.3 wt% gain between 5% RH and 55% RH suggesting Form A is non-hygroscopic from 5-55% RH. A loss of 1.8 wt% was observed between 55% RH and 65% RH possibly due to water displacing ethanol. After 65% RH, the sample gained 3.8 wt% between 65% RH and 95% RH. Notably, the sample mass did not meet the equilibrium criteria between 85% RH and 95% RH and all RH intervals during the desorption process. Weight loss (~7.6 wt%) was observed between 95% RH and 5% RH (i.e., desorption). After DVS analysis, it was noted that the sample had deliquesced.

[0139] Samples of Compound 1-ethanolate Form A were exposed to elevated RH (75%, 85% and 97%) at room temperature for approximately 3 hours and 24 hours (Table 8). After 3 hours, no deliquescence was observed at 75% RH, the sample appeared wet with solids present at 85% RH, and deliquescence was observed at 97% RH with minor birefringent solids present. After 24 hours, samples exposed to 85% RH and 97% RH deliquesced and the sample at 75% RH began deliquescing.

**Table 8. Time course of water absorption for Compound 1-ethanolate Form A under increasing relative humidities.**

| Elap Time<br>(min) | Weight<br>(mg) | Weight<br>% chg | Sample Temp<br>°C | Sample RH<br>% |
|--------------------|----------------|-----------------|-------------------|----------------|
| 0.1                | 14.448         | 0.000           | 25.18             | 0.99           |
| 21.1               | 14.441         | -0.043          | 25.19             | 5.15           |
| 39.7               | 14.447         | -0.003          | 25.19             | 14.86          |
| 51.8               | 14.455         | 0.051           | 25.20             | 24.90          |
| 64.8               | 14.465         | 0.120           | 25.19             | 34.83          |
| 78.3               | 14.479         | 0.214           | 25.19             | 44.87          |
| 91.2               | 14.493         | 0.316           | 25.18             | 54.86          |
| 281.1              | 14.232         | -1.494          | 25.18             | 65.03          |
| 294.7              | 14.279         | -1.170          | 25.20             | 74.65          |
| 356.0              | 14.513         | 0.451           | 25.19             | 84.85          |
| 543.7              | 14.782         | 2.311           | 25.19             | 94.83          |
| 731.2              | 14.539         | 0.633           | 25.19             | 85.19          |
| 918.9              | 14.347         | -0.694          | 25.19             | 74.98          |
| 1106.5             | 14.200         | -1.716          | 25.19             | 65.14          |
| 1296.4             | 14.073         | -2.592          | 25.19             | 54.99          |
| 1483.9             | 13.970         | -3.308          | 25.19             | 45.11          |
| 1671.4             | 13.882         | -3.916          | 25.19             | 35.03          |
| 1859.0             | 13.807         | -4.432          | 25.19             | 25.06          |
| 2044.7             | 13.742         | -4.883          | 25.19             | 14.87          |
| 2228.6             | 13.686         | -5.275          | 25.19             | 5.67           |

[0140] A separate DVS analysis using a stepped increase in relative humidity revealed that the mass increased by 0.3 wt.-% for Form A from 0% RH to 40% RH. At higher humidities, a decrease in mass was observed, due to loss of ethanol from the boronate ester complex. However, up to 60% r.h., the material retained its predominant crystal structure for at least four hours.

**Example 6. Mass Spectrometric Analyses of Compound 1-ethanolate Form A. Evidence for the conversion of Compound 1-ethanolate to ((2-ethylbutanoyl)oxy)methyl (*R*)-2-hydroxy-3-propionamido-3,4-dihydro-2*H*-benzo[*e*][1,2]oxaborinine-8-carboxylate (Compound 1) in aqueous solution.**

[0141] Mass spectrometric (MS) analyses were performed to confirm the structure of Compound 1-ethanolate Form A, and evaluate the ability of EtOH to dissociate from Compound 1-ethanolate in water. Compound 1-ethanolate Form A, and an amorphous preparation of ((2-ethylbutanoyl)oxy)methyl (*R*)-2-hydroxy-3-propionamido-3,4-dihydro-2*H*-benzo[*e*][1,2]oxaborinine-8-carboxylate were diluted in absolute EtOH or water and analyzed by high-resolution mass spectrometry. A sample of amorphous ((2-ethylbutanoyl)oxy)methyl (*R*)-2-hydroxy-3-propionamido-

3,4-dihydro-2*H*-benzo[*e*][1,2]oxaborinine-8-carboxylate, dissolved in absolute EtOH, was spiked with water prior to analysis. The mass spectrum of Compound 1-ethanolate Form A diluted in absolute EtOH showed major peaks consistent with sodiated Compound 1-ethanolate ( $M+Na$ )<sup>+</sup> at nominal 442 Da, and a sodium bound dimer of Compound 1-ethanolate ( $2M+Na$ )<sup>+</sup> at nominal 861 Da. The exact mass observed for sodiated Compound 1-ethanolate was 442.2007 (difference = 1.4 ppm vs. theoretical: C<sub>21</sub>H<sub>30</sub>BNO<sub>7</sub>Na<sup>+</sup>: 442.2013 Da).

[0142] The mass spectrum of Compound 1-ethanolate diluted in water showed major peaks at nominal 414 Da ( $M+Na$ )<sup>+</sup>, 787 Da ( $2M-H_2O+Na$ )<sup>+</sup>, 805 Da ( $2M+Na$ )<sup>+</sup>, 1178 Da ( $3M-H_2O+Na$ )<sup>+</sup>, and 1552 Da ( $4M-2H_2O+Na$ )<sup>+</sup> corresponding to ((2-ethylbutanoyl)oxy)methyl (*R*)-2-hydroxy-3-propionamido-3,4-dihydro-2*H*-benzo[*e*][1,2]oxaborinine-8-carboxylate (Compound 1).

[0143] The mass spectrum of ((2-ethylbutanoyl)oxy)methyl (*R*)-2-hydroxy-3-propionamido-3,4-dihydro-2*H*-benzo[*e*][1,2]oxaborinine-8-carboxylate, amorphous, diluted in absolute EtOH showed major peaks at nominal 442 Da and 861 Da, corresponding to sodiated Compound 1-ethanolate ( $M+Na$ )<sup>+</sup> and a sodium bound dimer of Compound 1-ethanolate ( $2M+Na$ )<sup>+</sup>, respectively. This is the same result as observed for Compound 1-ethanolate when diluted in EtOH and is likely due to ethyl (boron) ester formation, i.e., azeotropic removal of water, during the electrospray ionization process.

[0144] The mass spectrum of ((2-ethylbutanoyl)oxy)methyl (*R*)-2-hydroxy-3-propionamido-3,4-dihydro-2*H*-benzo[*e*][1,2]oxaborinine-8-carboxylate, amorphous, dissolved in absolute EtOH then spiked with water shows major peaks at nominal 414 Da ( $M+Na$ )<sup>+</sup>, 787 Da ( $2M-H_2O+Na$ )<sup>+</sup>, 805 Da ( $2M+Na$ )<sup>+</sup>, 1178 Da ( $3M-H_2O+Na$ )<sup>+</sup>, and 1552 Da ( $4M-2H_2O+Na$ )<sup>+</sup>. These correspond to sodiated ((2-ethylbutanoyl)oxy)methyl (*R*)-2-hydroxy-3-propionamido-3,4-dihydro-2*H*-benzo[*e*][1,2]oxaborinine-8-carboxylate ( $M+Na$ )<sup>+</sup>, ( $2M-H_2O+Na$ )<sup>+</sup>, ( $2M+Na$ )<sup>+</sup>, ( $3M-H_2O+Na$ )<sup>+</sup>, and ( $4M-2H_2O+Na$ )<sup>+</sup>; respectively. These are the same results observed for the sample of Compound 1-ethanolate Form A diluted in water, suggesting that Compound 1-ethanolate was rapidly converted to the free boronic acid ((2-ethylbutanoyl)oxy)methyl (*R*)-2-hydroxy-3-propionamido-3,4-dihydro-2*H*-benzo[*e*][1,2]oxaborinine-8-carboxylate in the presence of water.

#### Example 6. Preparation of Compound 1-ethanolate Form B.

[0145] A unique crystalline material, designated Form B, was observed from four experiments as mixtures with Compound 1-ethanolate Form A: 1) a heat/cool experiment of Compound 1-ethanolate in 5% EtOH in heptane; 2) stirring a solution that resulted from the addition of heptane to a solution of Compound 1-ethanolate in DCM; 3) stirring a hazy solution that resulted from the addition of cyclohexane to a solution produced after cooling a Compound 1-ethanolate solution in EtOAc:cyclohexane (1:3 v/v); and, 4) stirring a sample resulting from addition of heptane to an anisole solution containing Compound 1-ethanolate.

[0146] The infrared spectrum of Form B with minor Form A, was obtained. An overlay of the FT-IR spectra for Form B and Form A is shown in FIG. 8.

[0147] Compound 1-ethanolate Form B was further analyzed by Raman Spectroscopy, FIG. 9A. the peaks are shown in the table below:

| Peak | Wavenumber (cm <sup>-1</sup> ) | Peak | Wavenumber (cm <sup>-1</sup> ) | Peak | Wavenumber (cm <sup>-1</sup> ) |
|------|--------------------------------|------|--------------------------------|------|--------------------------------|
| 1    | 3073                           | 10   | 1429                           | 19   | 944                            |
| 2    | 2967                           | 11   | 1367                           | 20   | 918                            |
| 3    | 2935                           | 12   | 1345                           | 21   | 895                            |
| 4    | 2879                           | 13   | 1322                           | 22   | 844                            |
| 5    | 2834                           | 14   | 1249                           | 23   | 805                            |
| 6    | 2744                           | 15   | 1171                           | 24   | 753                            |
| 7    | 1740                           | 16   | 1150                           | 25   | 636                            |
| 8    | 1589                           | 17   | 1108                           | 26   | 556                            |
| 9    | 1455                           | 18   | 1018                           | 27   | 217                            |

[0148] An overlay of the Raman spectra of Form B and Form A is presented in FIG. 9B.

#### Example 7. XRPD characterization of Compound 1-ethanolate Form B.

[0149] The indexed XRPD pattern of Compound 1-ethanolate, Form B with minor Form A is illustrated in FIG. 10. Agreement between the allowed peak positions, marked with bars, and the observed peaks indicates a consistent unit cell determination. Successful indexing of the pattern indicates that the sample is composed primarily of a single crystalline phase. However, very minor peaks at 6.10°, 9.60°, 9.84°, and 10.05° are inconsistent with the allowed peaks for the indexed XRPD pattern of Form B thus suggesting the presence of an additional crystalline phase, specifically Form A.

| Bravais Type                  | Primitive Monoclinic |
|-------------------------------|----------------------|
| a [Å]                         | 11.958               |
| b [Å]                         | 11.383               |
| c [Å]                         | 17.329               |
| $\alpha$ [deg]                | 90                   |
| $\beta$ [deg]                 | 92.40                |
| $\gamma$ [deg]                | 90                   |
| Volume [Å <sup>3</sup> /cell] | 2356.8               |
| Chiral Contents?              | Chiral               |
| Extinction Symbol             | P 1 2 <sub>1</sub> 1 |
| Space Group(s)                | P2 <sub>1</sub> (4)  |

**Example 8. Thermal analysis of Compound 1-ethanolate Form B.**

[0150] Thermal analysis (DSC) revealed that Form B exhibited a small, broad feature at 77.7 °C (peak maximum) followed by an endotherm at 116.9 °C (peak maximum) which is likely attributable to melting (FIG. 11). A weight loss of 1.2% was observed between 23.6 °C and 125.0 °C by TGA analysis.

**Example 9: Dynamic Vapor Sorption (DVS) Analysis of Compound 1-ethanolate Form B.**

[0151] DVS analysis of Compound 1-ethanolate Form B (with minor Form A) was conducted from 5% RH to 95% RH and back to 5% RH at 10% RH increments (FIG. 12). The DVS isotherm of Form B is qualitatively similar to that of Form A. Form B lost 0.2 wt% upon equilibration at ~5% RH. With increasing RH, the sample showed ~0.5 wt% gain between 5% RH and 45% RH. A weight loss of 1.1% was observed between 45% RH and 55% RH, possibly due to the displacement of the ethanol with water. After 55% RH, the sample gained 3.3 wt% between 55% RH and 95% RH. The sample mass did not meet the equilibrium criteria between 85% RH and 95% RH and all RH intervals during the desorption process to 15% RH. Weight loss (~5.8 wt%) was observed during desorption from 95% RH to 5% RH. Following DVS analysis, it was noted that the sample appeared to have deliquesced.

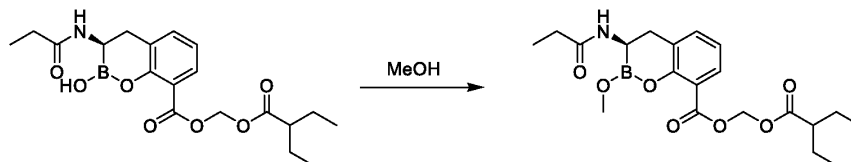
[0152] A separate DVS analysis using a stepped increase in relative humidity revealed that the mass increased by 0.4 wt.% for Form B from 0% RH to 40% RH. At higher humidities, a decrease in mass was observed, due to loss of ethanol from the boronate ester complex. However, up to 60% r.h., the material retained its predominant crystal structure for at least four hours.

**Example 10. Interconversion Slurries.**

[0153] The difference in free energy between solid phases of the same composition (i.e. true polymorphs) is related to their relative solubilities, with the most stable polymorph having the lowest solubility in any solvent compared to a metastable polymorph. Therefore, a saturated solution with respect to the most stable form is undersaturated with respect to the less stable form. In the presence of seeds of different polymorphs, the less stable polymorph will therefore dissolve over time, resulting in further growth of the most stable form.

[0154] Solvent-mediated slurry interconversion experiments using seeds of different polymorphs were conducted to determine the most stable form of Compound 1-ethanolate. Saturated solutions of Compound 1-ethanolate were prepared in 3% DCM in heptane and 5% EtOH in heptane. Approximately equal amounts of Form A, and Form B (containing a minor amount of Form A) were added to the filtered saturated solutions, and the suspensions were slurried at room temperature for ~2 weeks, and the isolated solids were observed by polarized light microscopy (PLM) and analyzed by XRPD. XRPD patterns of the solids isolated from both slurries were consistent with Form A. These data suggest Form A is the stable form at room temperature.

**Example 11: Preparation and Characterization of ((2-Ethylbutanoyl)oxy)methyl (R)-2-methoxy-3-propionamido-3,4-dihydro-2H-benzo[e][1,2]oxaborinine-8-carboxylate (Compound 1-methanolate)**

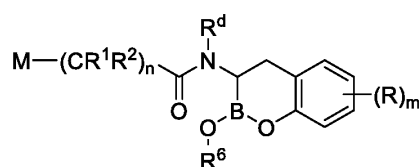


**[0155]** ((2-Ethylbutanoyl)oxy)methyl (*R*)-2-hydroxy-3-propionamido-3,4-dihydro-2*H*-benzo[e][1,2]oxaborinine-8-carboxylate (Compound 1) in methanol yielded ((2-Ethylbutanoyl)oxy)methyl (*R*)-2-methoxy-3-propionamido-3,4-dihydro-2*H*-benzo[e][1,2]oxaborinine-8-carboxylate (Compound 1-methanolate). FIG. 13 shows the x-ray structure of Compound 1-methanolate.

## CLAIMS

## WHAT IS CLAIMED:

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



Formula (I);

wherein:

- M is hydrogen, halogen,  $-\text{CD}_3$ ,  $-\text{CF}_3$ ,  $-\text{CN}$ ,  $-\text{OR}^4$ ,  $-\text{C}(=\text{O})\text{R}^4$ ,  $-\text{C}(=\text{O})\text{NR}^4\text{R}^5$ ,  $-\text{SR}^4$ ,  $-\text{S}(=\text{O})\text{R}^4$ ,  $-\text{S}(=\text{O})_2\text{R}^4$ ,  $-\text{S}(=\text{O})_2\text{NR}^4\text{R}^5$ ,  $-\text{NR}^4\text{R}^5$ ,  $-\text{NR}^4\text{C}(=\text{O})\text{R}^5$ ,  $-\text{NR}^4\text{C}(=\text{O})\text{NR}^4\text{R}^5$ ,  $-\text{NR}^4\text{S}(=\text{O})_2\text{R}^5$ , or alkynyl;
- each  $\text{R}^1$  and  $\text{R}^2$  is independently hydrogen, deuterium, halogen,  $-\text{OR}^4$ ,  $-\text{SR}^4$ ,  $-\text{NR}^4\text{R}^5$ , optionally substituted  $\text{C}_1$ - $\text{C}_6$  alkyl, optionally substituted  $\text{C}_1$ - $\text{C}_6$  haloalkyl, optionally substituted  $\text{C}_1$ - $\text{C}_6$  hydroxyalkyl, or optionally substituted  $\text{C}_1$ - $\text{C}_6$  aminoalkyl;
- or  $\text{R}^1$  and  $\text{R}^2$  are taken together with the carbon to which they are attached to form an optionally substituted cycloalkyl;
- or when n is at least 2, two  $\text{R}^1$  on adjacent carbons are taken together to form a double bond;
- or when n is at least 2, two  $\text{R}^1$  and two  $\text{R}^2$  on adjacent carbons are taken together to form a triple bond;
- n is 0, 1, 2, 3, 4, 5, or 6;
- each R is independently  $-\text{COOR}^3$ ,  $\text{R}^a$ ,  $\text{R}^b$ , or  $\text{R}^c$ ;
- m is 0, 1, 2, 3, or 4;
- $\text{R}^3$  is  $\text{R}^{31}$ ,  $-(\text{R}^{30})_q\text{OR}^{31}$ ,  $-(\text{R}^{30})_q\text{O}(\text{R}^{30})_q\text{R}^{31}$ ,  $-\text{R}^{30}\text{OC}(\text{O})\text{R}^{31}$ ,  $-\text{R}^{30}\text{OC}(\text{O})\text{OR}^{31}$ ,  $-\text{R}^{30}\text{OC}(\text{O})\text{NHR}^{31}$ , or  $-\text{R}^{30}\text{OC}(\text{O})\text{N}(\text{R}^{31})_2$ ;
- each q is independently 2, 3, 4, 5, or 6;
- each  $\text{R}^{30}$  is independently  $-\text{CH}_2-$ ,  $-\text{CH}(\text{CH}_3)-$ ,  $-\text{C}(\text{CH}_3)_2-$ , or optionally substituted 1,1-cyclopropylene;
- each  $\text{R}^{31}$  is independently optionally substituted  $\text{C}_1$ - $\text{C}_{12}$  alkyl, optionally substituted  $\text{C}_1$ - $\text{C}_{12}$  haloalkyl, optionally substituted  $\text{C}_1$ - $\text{C}_{12}$  hydroxyalkyl, optionally substituted  $\text{C}_1$ - $\text{C}_{12}$  aminoalkyl, optionally substituted  $\text{C}_1$ - $\text{C}_{12}$  alkoxyalkyl, optionally substituted  $\text{C}_2$ - $\text{C}_{12}$  alkenyl, optionally substituted  $\text{C}_2$ - $\text{C}_{12}$  alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted  $(\text{C}_1$ - $\text{C}_6$  alkyl)cycloalkyl, optionally substituted  $(\text{C}_1$ - $\text{C}_6$  alkyl)heterocycloalkyl, optionally substituted  $(\text{C}_1$ - $\text{C}_6$  alkyl)aryl, or optionally substituted  $(\text{C}_1$ - $\text{C}_6$  alkyl)heteroaryl; or
- two  $\text{R}^{31}$  are taken together with the nitrogen to which they are attached to form a heterocycloalkyl;

$R^a$ ,  $R^b$ , and  $R^c$  are independently hydrogen, deuterium, halogen,  $-OR^4$ ,  $-NR^4R^5$ ,  $-SR^4$ , optionally substituted  $C_1$ - $C_6$  alkyl, optionally substituted  $C_1$ - $C_6$  haloalkyl, optionally substituted  $C_1$ - $C_6$  hydroxyalkyl, optionally substituted  $C_1$ - $C_6$  aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

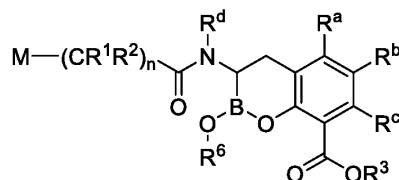
$R^d$  is hydrogen or optionally substituted  $C_1$ - $C_6$  alkyl;

$R^4$  and  $R^5$  are independently hydrogen,  $-OH$ ,  $-CN$ , optionally substituted  $C_1$ - $C_6$  alkyl, optionally substituted  $C_1$ - $C_6$  haloalkyl, optionally substituted  $C_1$ - $C_6$  hydroxyalkyl, optionally substituted  $C_1$ - $C_6$  aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

or  $R^4$  and  $R^5$  taken together with the nitrogen to which they are attached to form an optionally substituted heterocycloalkyl; and

$R^6$  is optionally substituted  $C_1$ - $C_6$  alkyl, optionally substituted  $C_1$ - $C_6$  haloalkyl, optionally substituted  $C_1$ - $C_6$  hydroxyalkyl, optionally substituted  $C_1$ - $C_6$  aminoalkyl, optionally substituted  $C_1$ - $C_6$  deutoalkyl, optionally substituted  $C_1$ - $C_6$  heteroalkyl, optionally substituted  $C_2$ - $C_6$  alkenyl, optionally substituted  $C_2$ - $C_6$  alkynyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted  $(C_1$ - $C_6$  alkyl)cycloalkyl, optionally substituted  $(C_1$ - $C_6$  alkyl)heterocycloalkyl, optionally substituted  $(C_1$ - $C_6$  alkyl)aryl, or optionally substituted  $(C_1$ - $C_6$  alkyl)heteroaryl.

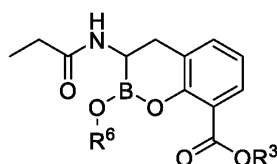
2. The compound of claim 1, wherein the compound is of Formula (Ia), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (Ia).

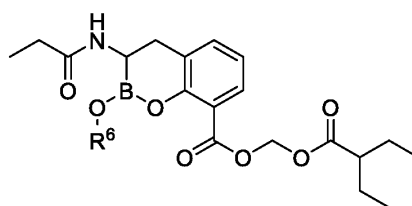
3. The compound of claim 1 or 2, wherein  $R^a$ ,  $R^b$ , and  $R^c$  are independently hydrogen, halogen,  $-OR^4$ ,  $-NR^4R^5$ ,  $-SR^4$ , or optionally substituted  $C_1$ - $C_6$  alkyl.
4. The compound of any one of claims 1-3, wherein  $R^a$ ,  $R^b$ , and  $R^c$  are independently hydrogen, halogen,  $-OH$ , or  $-OCH_3$ .
5. The compound of any one of claims 1-4, wherein  $R^a$ ,  $R^b$ , and  $R^c$  are hydrogen.
6. The compound of any one of claims 1-5, wherein  $R^d$  is hydrogen or  $C_1$ - $C_4$  alkyl.
7. The compound of any one of claims 1-6, wherein  $R^d$  is hydrogen.
8. The compound of any one of claims 1-7, wherein  $n$  is 0, 1, 2, or 3.

9. The compound of any one of claims 1-8, wherein n is 2.
10. The compound of any one of claims 1-8, wherein n is 1.
11. The compound of any one of claims 1-10, wherein each  $R^1$  and  $R^2$  are independently hydrogen, halogen, optionally substituted  $C_1$ - $C_6$  alkyl, or optionally substituted  $C_1$ - $C_6$  haloalkyl.
12. The compound of any one of claims 1-11, wherein each  $R^1$  and  $R^2$  are independently hydrogen or halogen.
13. The compound of any one of claims 1-12, wherein each  $R^1$  and  $R^2$  are hydrogen.
14. The compound of any one of claims 1-13, wherein M is hydrogen, -CN,  $-C(=O)R^4$ , or alkynyl.
15. The compound of any one of claims 1-14, wherein M is hydrogen.
16. The compound of any one of claims 1-15, wherein the compound is of Formula (Ib), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



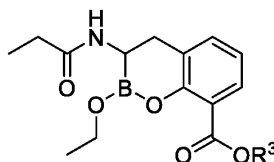
Formula (Ib).

17. The compound of any one of claims 1-16, wherein  $R^3$  is  $R^{31}$ .
18. The compound of any one of claims 1-16, wherein  $R^3$  is  $-R^{30}OC(O)R^{31}$  or  $-R^{30}OC(O)OR^{31}$ .
19. The compound of any one of claims 1-16, wherein  $R^3$  is  $-R^{30}OC(O)R^{31}$ .
20. The compound of any one of claims 1-19, wherein  $R^{30}$  is independently  $-CH_2-$  or  $-CH(CH_3)-$ .
21. The compound of any one of claims 1-20, wherein  $R^{30}$  is independently  $-CH_2-$ .
22. The compound of any one of claims 1-21, wherein each  $R^{31}$  is independently optionally substituted  $C_1$ - $C_{12}$  alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted aryl.
23. The compound of any one of claims 1-21, wherein each  $R^{31}$  is independently optionally substituted  $C_1$ - $C_{12}$  alkyl.
24. The compound of any one of claims 1-23, wherein the compound is of Formula (Ic), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



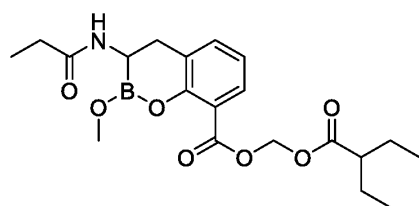
Formula (Ic).

25. The compound of any one of claims 1-24, wherein  $R^6$  is  $C_1$ - $C_6$  alkyl.
26. The compound of any one of claims 1-25, wherein  $R^6$  is methyl, ethyl, propyl, or butyl.
27. The compound of any one of claims 1-16, wherein the compound is of Formula (Id), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



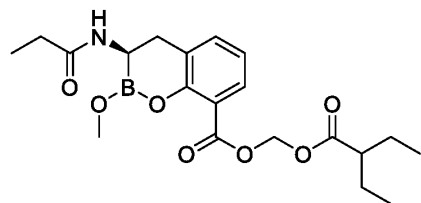
Formula (Id).

28. The compound of claim 1, wherein the compound is:



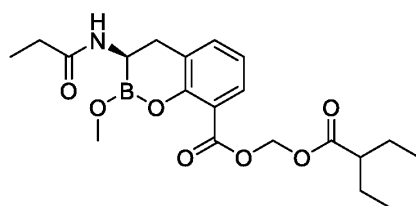
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

29. The compound of claim 1, wherein the compound is:

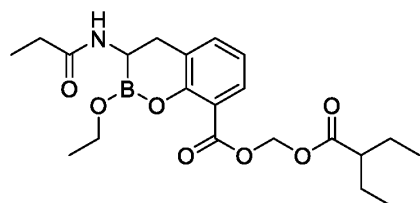


or a pharmaceutically acceptable salt or solvate thereof.

30. The compound of claim 1, wherein the compound is:

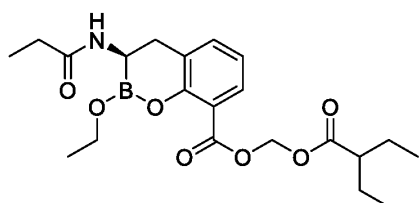


31. The compound of claim 1, wherein the compound is:



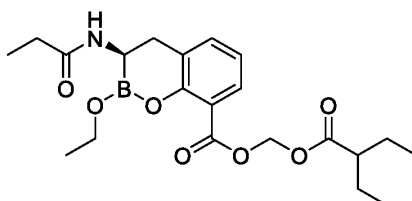
or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

32. The compound of claim 1, wherein the compound is:



or a pharmaceutically acceptable salt or solvate thereof.

33. The compound of claim 1, wherein the compound is:



34. A crystalline form of the compound of claim 33.

35. The crystalline form of claim 34, wherein the crystalline form has an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in FIG. 4.

36. The crystalline form of claim 34, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern comprising characteristic peaks at about  $6.1^{\circ} \pm 0.1^{\circ} 2\theta$ , about  $9.9^{\circ} \pm 0.1^{\circ} 2\theta$ , and about  $16.0^{\circ} \pm 0.1^{\circ} 2\theta$ .

37. The crystalline form of claim 36, wherein the X-ray powder diffraction (XRPD) pattern further comprises characteristic peaks at about  $19.3^{\circ} \pm 0.1^{\circ} 2\theta$ , about  $6.8^{\circ} \pm 0.1^{\circ} 2\theta$ , and about  $17.9^{\circ} \pm 0.1^{\circ} 2\theta$ .

38. The crystalline form of claim 36 or 37, wherein the X-ray powder diffraction (XRPD) pattern further comprises characteristic peaks at about  $14.3^{\circ} \pm 0.1^{\circ} 2\theta$  and about  $21.2^{\circ} \pm 0.1^{\circ} 2\theta$ .
39. The crystalline form of claim 34, wherein the crystalline form has a DSC thermogram substantially the same as shown in FIG. 6.
40. The crystalline form of claim 34, wherein the crystalline form has a DSC thermogram with a broad endotherm having an onset at about  $112.8^{\circ} \text{C}$ .
41. The crystalline form of claim 34, wherein the crystalline form has a  $^1\text{H}$  spectrum substantially the same as shown in FIG. 1A.
42. The crystalline form of claim 34, wherein the crystalline form has a  $^{13}\text{C}$  spectrum substantially the same as shown in FIG. 1B.
43. The crystalline form of claim 34, wherein the crystalline form has an FT-IR spectrum substantially the same as shown in FIG. 2.
44. The crystalline form of claim 34, wherein the crystalline form has a Raman spectrum substantially the same as shown in FIG. 3.
45. The crystalline form of claim 34, wherein the crystalline form has an X-Ray powder diffraction (XRPD) pattern substantially the same as shown in FIG. 10.
46. The crystalline form of claim 34, wherein the crystalline form has an X-ray powder diffraction (XRPD) pattern comprising characteristic peaks at about  $9.3^{\circ} \pm 0.1^{\circ} 2\theta$ , about  $12.9^{\circ} \pm 0.1^{\circ} 2\theta$ , and about  $21.5^{\circ} \pm 0.1^{\circ} 2\theta$ .
47. The crystalline form of claim 46, wherein the X-ray powder diffraction (XRPD) pattern further comprises characteristic peaks at about  $8.8^{\circ} \pm 0.1^{\circ} 2\theta$ , about  $14.6^{\circ} \pm 0.1^{\circ} 2\theta$ , and about  $17.3^{\circ} \pm 0.1^{\circ} 2\theta$ .
48. The crystalline form of claim 34, wherein the crystalline form has a DSC thermogram substantially the same as shown in FIG. 11.
49. The crystalline form of claim 34, wherein the crystalline form has a DSC thermogram with a broad endotherm having an onset at about  $116.9^{\circ} \text{C}$ .
50. The crystalline form of claim 34, wherein the crystalline form has an FT-Raman spectrum substantially the same as shown in FIG. 9A.
51. A pharmaceutical composition comprising a compound of any one of claims 1-50, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable excipient.
52. The pharmaceutical composition of claim 51, further comprising a beta-lactam antibiotic.

53. The pharmaceutical composition of claim 52, wherein the beta-lactam antibiotic is a penicillin, a cephalosporin, a carbapenem, a monobactam, or a combination thereof.
54. A method of treating a bacterial infection in a subject, comprising administering to the subject a compound of any one of claims 1-50 in combination with a therapeutically effective amount of a beta-lactam antibiotic.
55. The method of claim 54, wherein the beta-lactam antibiotic is ceftibuten, or a salt thereof.