[0031] The ability to adjust biological production of energy has applications beyond the diseases described above. Various other disorders can result in suboptimal levels of energy biomarkers (sometimes also referred to as indicators of energetic function), such as ATP levels. Treatments for these disorders are also needed, in order to modulate one or more energy biomarkers to improve the health of the patient. In other applications, it can be desirable to modulate certain energy biomarkers away from their normal values in an individual that is not suffering from disease. For example, if an individual is undergoing an extremely strenuous undertaking, it can be desirable to raise the level of ATP in that individual.

[0032] Certain polymorphic or amorphous forms of a drug can have advantageous characteristics versus other forms; for example, increased stability, increased solubility, better handling properties, lack of associated toxic solvents, and increased purity.

[0033] Example 16 of PCT Application No. PCT/US2008/082374, published as WO 2009/061744 on May 14, 2009, describes a synthesis for racemic 2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide; this Example does not specifically describe the synthesis of any particular polymorphic or amorphous form for (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide or any particular stereoisomer thereof.

BRIEF SUMMARY OF THE INVENTION

[0034] The disclosure provides a polymorph of an anhydrate, a hydrate, or a solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, wherein the polymorph is selected from the group consisting of Form I, Form II, Form III, Form IV, Form V, and Form VI as described herein.

[0034a] In one aspect of the disclosure is an polymorph of an anhydrate, a hydrate, or a solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, wherein the polymorph is selected from the group consisting of Forms II and III; wherein a powder X-ray diffraction pattern for polymorph Form II comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.63, 10.85, 11.33, and 19.33; wherein a powder X-ray diffraction pattern for polymorph Form III comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.16, 14.02, 15.23, and 21.10; and wherein the XRPD pattern is generated at 25 °C.

[0035] The disclosure also provides a polymorph of an anhydrate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, wherein the polymorph is Form I as described herein. In some examples, the polymorph has a powder x-ray diffraction pattern substantially as shown in Figure 10. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 12.06, 17.03, and 17.26. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 12.06, 17.03, and 17.26. In some examples, a powder X-ray diffraction pattern for the

polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 12.06, 15.33, 17.03, and 17.26. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 12.06, 15.33, 17.03, 17.26, and 18,72. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, where in the angular positions may vary by ± 0.2: 12.06, 15.33, 17.03, 17.26, and 18.72. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 7.67, 10.75, 12.06, 15.33, 16.41, 17.03, 17.26, 18.72, 20.04, and 23.92. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 7.67, 10.75, 12.06, 15.33, 16.41, 17.03, 17.26, 18.72, 20.04, 20.64, 20.91, 21.14, 22.58, 23.13, 23.92, 24.19, 24.53, 27.21, and 27.56. In some embodiments, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 5.48, 7.67, 10.75, 12.06, 15.33, 16.41, 17.03, 17.26, 17.71, 17.94, 18.40, 18.72, 19.51, 20.04, 20.64, 20.91, 21.14, 21.55, 21.91, 22.25, 22.58, 23.13, 23.41, 23.92, 24.19, 24.53, 25.64, 26.13, 26.34, 27.21, 27.56, 28.01, 29.04, and 29.46. In some examples, including any of the foregoing examples, the angular positions may vary by ± 0.1. In some examples, including any of the foregoing examples, the angular positions may vary by ± 0.05. In some examples, including any of the foregoing examples, the angular positions may vary by ± 0.02. In some embodiments, including any of the foregoing examples, the polymorph is isolated. In some examples, including any of the foregoing examples, the polymorph is present in a composition, wherein the composition is essentially free of Forms II-VI, wherein Forms II-VI are described in Table A or Tables 3-7 respectively. In some examples, including any of the foregoing embodiments, the polymorph is present in a composition, wherein at least about 95% of the composition is the polymorph, exclusive of any solvents, carriers or excipients.

[0036] The disclosure also provides a polymorph of an anhydrate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, wherein the polymorph is Form V as described herein. In some examples, the polymorph has a powder x-ray diffraction pattern substantially as shown in a) or b) of Figure 30. In some examples, a

powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.61, 11.49, and 15.45. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.61, 11.49, and 15.45. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.61, 11.49, 15.45, and 23.96. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.61, 11.49, 14.80, 15.45, 23.96. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.61, 11.49, 12.93, 15.45, and 26.05. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.61, 11.49, 12.93, 14.80, 15.45, 16.53, 23.96, 24.54, and 26.05. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.61, 11.49, 12.93, 14.80, 15.45, 16.10, 16.34, 16.53, 20.18, 22.52, 22.86, 23.96, 24.54, and 26.05. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 6.91, 7.72, 9.61, 11.49, 11.86, 12.93, 13.19, 13.87, 14.80, 15.45, 16.10, 16.34, 16.53, 17.14, 17.85, 19.12, 19.85, 20.18, 21.00, 22.06, 22.52, 22.86, 23.09, 23.96, 24.54, 25.26, 26.05, and 26.90. In some examples, including any of the foregoing examples, the angular positions may vary by ± 0.1. In some examples, including any of the foregoing examples, the angular positions may vary by ± 0.05. In some examples, including any of the foregoing examples, the angular positions may vary by ± 0.02. In some examples, including any of the foregoing examples, the polymorph is isolated. In some examples, including any of the foregoing examples, the polymorph is present in a composition, wherein the composition is essentially free of Forms I-IV and-VI, wherein Forms I-IV and-VI are described in Table A or Tables 2, or 4-7 respectively. In some examples, including any of the foregoing examples, the polymorph is present in a composition, wherein at least about 95% of the composition is the polymorph, exclusive of any solvents, carriers or excipients.

[0037] The disclosure also provides a polymorph of a hydrate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, wherein the polymorph is Form III as described herein. In some examples, the polymorph has a powder x-ray diffraction pattern substantially as shown in a) or b) of Figure 20. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 14.02, 15.23, and 21.10. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 14.02, 15.23, and 21.10. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.16, 14.02, 15.23, and 21.10. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.16, 13.74, 14.02, 15.23, and 21.10. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.16, 14.02, 15.23, 21.10, and 22.69. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.16, 11.81, 13.74, 14.02, 15.23, 21.10, 22.69, and 23.90. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.16, 11.81, 13.74, 14.02, 15.23, 17.35, 21.10, 22.69, 23.15, 23.90, and 26.10. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.16, 11.53, 11.81, 12.68, 12.93, 13.74, 14.02, 15.23, 16.53, 17.35, 17.98, 18.54, 19.09, 20.23, 21.10, 21.93, 22.69, 23.15, 23.50, 23.90, 24.65, 25.09, 25.46, 25.79, 26.10, 27.79, 28.22, 28.93, and 29.33. In some examples, including any of the foregoing examples, the angular positions may vary by ± 0.1. In some examples, including any of the foregoing examples, the angular positions may vary by ± 0.05. In some examples, including any of the foregoing examples, the angular positions may vary by ± 0.02. In some examples, including any of the foregoing examples, the polymorph is isolated. In some examples, including any of the foregoing examples, the polymorph is present in a composition, wherein the composition

is essentially free of Forms I, II, IV, V, and VI, wherein Forms I, II, IV, V, and VI are described in Table A or Tables 2-3 and 5-7 respectively. In some examples, including any of the foregoing examples, the polymorph is present in a composition, wherein at least about 95% of the composition is the polymorph, exclusive of any solvents, carriers or excipients.

[0038] The disclosure also provides a polymorph of a solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, wherein the polymorph is Form II as described herein. In some examples, the polymorph has a powder x-ray diffraction pattern substantially as shown in a) or b) of Figure 15. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.63, 11.33, and 19.33. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.63, 11.33, 19.33. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.63, 11.33, 10.85, and 19.33. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: . 9.63, 11.33, 10.85, 19.33, and 17.3. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.63, 10.85, 11.33, 13.47, and 19.33. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 5.76, 8.04, 9.63, 10.85, 11.33, 11.97, 13.47, 14.75, 17.37, 17.71, and 19.33. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 5.76, 8.04, 9.63, 10.85, 11.33, 11.97, 13.47, 14.75, 16.42, 16.89, 17.37, 17.71, 19.33, 22.89, and 24.59. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 5.76, 6.72, 7.57, 8.04, 9.63, 10.85, 11.33, 11.97, 12.38, 13.13, 13.47, 14.75, 15.28, 16.42, 16.89, 17.37, 17.71, 18.17, 18.66, 19.33, 20.01, 20.29, 20.67, 20.90, 21.36, 21.54, 21.80, 22.55, 22.89, 23.27, 23.54, 23.87, 24.35, 24.59, 24.87, 25.29, 25.55, 25.89, 26.44, 27.49, 28.01, 28.39, and 29.17. In some examples, including any of the foregoing examples, the

angular positions may vary by ± 0.1. In some examples, including any of the foregoing examples, the angular positions may vary by ± 0.05. In some examples, including any of the foregoing examples, the angular positions may vary by ± 0.02. In some examples, including any of the foregoing examples, the polymorph is isolated. In some examples, including any of the foregoing examples, the polymorph is present in a composition, wherein the composition is essentially free of Forms I, and III-VI, wherein Forms I, and III-VI are described in Table A or Tables 2-4 and 6-7 respectively. In some examples, including any of the foregoing examples, the polymorph is present in a composition, wherein at least about 95% of the composition is the polymorph, exclusive of any solvents, carriers or excipients.

[0039] The disclosure also provides a polymorph of a solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, wherein the polymorph is Form IV as described herein. In some examples, the polymorph has a powder x-ray diffraction pattern substantially as shown in a), b), or c) of Figure 25. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 4.31, 12.97, and 13.20. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 4.31, 12.97, 13.20. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 4.31, 8.76, 12.97, and 13.20. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 0.2: 4.31, 8.76, 12.97, 13.20, 16.66. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 4.31, 8.76, 12.97, 13.20, and 16.66. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 4.31, 7.94, 8.76, 12.97, 13.20, 16.66, 17.33, and 20.57. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 4.31, 7.94, 8.76, 12.97, 13.20, 15.08, 16.66, 17.33, 19.09, 20.57, and 21.58. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular

positions, wherein the angular positions may vary by ± 0.2: 4.31, 5.77, 6.28, 7.53, 7.94, 8.76, 9.39, 9.87, 10.54, 11.07, 11.68, 12.02, 12.28, 12.97, 13.20, 13.52, 14.40, 15.08, 15.90, 16.66, 16.96, 17.33, 17.59, 18.77, 19.09, 19.74, 20.27, 20.57, 21.09, 21.58, 22.81, 23.23, 24.01, 24.65, and 25.60. In some examples, including any of the foregoing examples, the angular positions may vary by ± 0.1. In some examples, including any of the foregoing examples, the angular positions may vary by ± 0.05. In some examples, including any of the foregoing examples, the angular positions may vary by ± 0.02. In some examples, including any of the foregoing examples, the polymorph is isolated. In some examples, including any of the foregoing examples, the polymorph is present in a composition, wherein the composition is essentially free of Forms I-III and V-VI, wherein Forms I-III and V-VI are described in Table A or Tables 2-5 and 7 respectively. In some examples, including any of the foregoing examples, the polymorph is present in a composition, wherein at least about 95% of the composition is the polymorph, exclusive of any solvents, carriers or excipients.

[0040] The disclosure also provides a polymorph of a solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, wherein the polymorph is Form VI as described herein. In some examples, the polymorph has a powder x-ray diffraction pattern substantially as shown in a) of Figure 33. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 6.27, 9.91, and 12.94. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 6.27, 9.91, and 12.94. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 6.27, 9.91, 12.94, and 15.71. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 6.27, 9.91, 12.94, 15.71, and 19.13. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 6.27, 9.41, 9.91, 12.94, and 13.29. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 6.27, 8.85, 9.41, 9.91, 12.94, 13.29, 16.67, and 19.13. In some examples, a powder X-ray diffraction pattern for the polymorph

comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 4.39, 6.27, 8.85, 9.41, 9.91, 11.32, 12.94, 13.29, 14.03, 16.67, 19.13, 20.76, and 22.06. In some examples, a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 4.39, 6.27, 7.00, 8.62, 8.85, 9.41, 9.91, 11.32, 11.50, 12.25, 12.56, 12.94, 13.29, 14.03, 14.82, 15.10, 15.44, 15.71, 16.01, 16.67, 16.91, 17.33, 17.59, 18.33, 18.75, 19.13, 20.25, 20.76, 21.68, 22.06, 22.27, 22.61, 22.94, 24.01, 24.33, 24.65, 25.48, 26.05, 28.63, and 29.18. In some examples, including any of the foregoing examples, the angular positions may vary by ± 0.1. In some examples, including any of the foregoing examples, the angular positions may vary by ± 0.05. In some examples, including any of the foregoing examples, the angular positions may vary by ± 0.02. In some examples, including any of the foregoing examples, the polymorph is isolated. In some examples, including any of the foregoing examples, the polymorph is present in a composition, wherein the composition is essentially free of Forms I-V, wherein Forms I-V are described in Table A or Tables 2-6 respectively. In some examples, including any of the foregoing examples, the polymorph is present in a composition, wherein at least about 95% of the composition is the polymorph, exclusive of any solvents, carriers or excipients.

[0041] The disclosure also provides a composition comprising amorphous (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide. In some examples, the amorphous form is isolated. In some examples, the composition is essentially free of Forms I-VI, wherein Forms I-VI are described in Table A or Tables 2-7 respectively. In some examples, including any of the foregoing examples, at least about 95% of the composition is amorphous (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, exclusive of any solvents, carriers or excipients.

[0041a] In another aspect of the disclosure is a composition comprising the polymorph as defined herein, wherein the composition is essentially free of Forms I, II, IV, V, and VI, wherein a powder X-ray diffraction pattern for polymorph Form I comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 12.06, 15.33 17.03, and 17.26; wherein a powder X-ray diffraction pattern for polymorph Form II comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.63, 10.85, 11.33, and 19.33; wherein a powder X-ray diffraction pattern for polymorph Form IV comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 8.76, 12.97, 13.20, and 16.66; wherein a powder X-ray diffraction pattern for polymorph Form V comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.61, 11.49, 12.93, and 15.45; and wherein a powder X-ray diffraction pattern for polymorph Form

VI comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 6.27, 9.91, 12.94, and 15.71.

[0041b] In another aspect of the disclosure is a composition comprising the polymorph as defined herein, wherein at least about 95% by mole of the composition is the polymorph Form III, exclusive of any solvents, carriers or excipients.

[0041c] In another aspect of the disclosure is a composition comprising the polymorph as defined herein, wherein the composition is essentially free of Forms I, III-VI, wherein a powder X-ray diffraction pattern for polymorph Form I comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 12.06, 15.33 17.03, and 17.26; wherein a powder X-ray diffraction pattern for polymorph Form III comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.16, 14.02, 15.23, and 21.10; wherein a powder X-ray diffraction pattern for polymorph Form IV comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 8.76, 12.97, 13.20, and 16.66; wherein a powder X-ray diffraction pattern for polymorph Form V comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.61, 11.49, 12.93, and 15.45; and wherein a powder X-ray diffraction pattern for polymorph Form VI comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 6.27, 9.91, 12.94, and 15.71.

[0041d] In another aspect of the disclosure is a composition comprising the polymorph as defined herein, wherein at least about 95% by mole of the composition is the polymorph Form II, exclusive of any solvents, carriers or excipients.

[0042] The disclosure also provides a pharmaceutical composition comprising a polymorphic or amorphous form of an anhydrate, a hydrate, or a solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, or composition comprising such form, as described herein, including any of the foregoing or hereafter examples, and a pharmaceutically acceptable carrier. In some examples, the form is polymorph Form I. In some examples, the form is polymorph Form II. In some examples, the form is polymorph Form III. In some examples, the form is polymorph Form IV. In some examples, the form is polymorph Form V. In some examples, the

form is polymorph Form VI. In some examples, the form is amorphous. In some examples, the pharmaceutical composition has an HPLC purity of more than about 95% for the anhydrate, hydrate, or solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, exclusive of any solvents, carriers or excipients. In some examples, the pharmaceutical composition has an HPLC purity of more than about 99% for the anhydrate, hydrate, or solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, exclusive of any solvents, carriers or excipients. In some examples, the pharmaceutical composition has an HPLC purity of more than about 99.9% for the anhydrate, hydrate, or solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, exclusive of any solvents, carriers or excipients. HPLC purity % refers to the proportional area of a given compound's HPLC peak with respect to the area of all peaks in a given HPLC spectrum. HPLC % is calculated by dividing the area of a compound peak by the area of all peaks, in a HPLC spectrum, and multiplying this quotient by one-hundred.

[0043] The disclosure also provides a pharmaceutical composition comprising an active agent and a pharmaceutically acceptable carrier, wherein the active agent consists of, or consists essentially of, a polymorphic or amorphous form of an anhydrate, a hydrate, or a solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide as described herein. In some examples, the form is polymorph Form I. In some examples, the form is polymorph Form II. In some examples, the form is polymorph Form III. In some examples, the form is polymorph Form IV. In some examples, the form is polymorph Form V. In some examples, the form is polymorph Form VI. In some examples, the form is amorphous.

[0043a] In another aspect of the disclosure is a pharmaceutical composition comprising the polymorph as defined herein, or the composition as defined herein, and a pharmaceutically acceptable carrier.

[0044] The disclosure also provides a method of treating or suppressing an oxidative stress disorder, modulating one or more energy biomarkers, normalizing one or more energy biomarkers, or enhancing one or more energy biomarkers, comprising administering to an individual in need thereof a therapeutically effective amount or effective amount of a polymorphic or amorphous form of an anhydrate, a hydrate, or a solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, or composition comprising such form, as described herein, including any of the foregoing or hereafter examples. The method can use any individual polymorphic or amorphous form of the invention as described herein, or a combination of such. In some examples, the form is

polymorph Form I. In some examples, the form is polymorph Form II. In some examples, the form is polymorph Form III. In some examples, the form is polymorph Form IV. In some examples, the form is polymorph Form V. In some examples, the form is polymorph Form VI. In some examples, the form is amorphous. In some examples, including any of the foregoing examples, the anhydrate, hydrate, or solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide is administered in a pharmaceutical composition comprising the polymorphic or amorphous form and a pharmaceutically acceptable carrier. In some examples, including any of the foregoing examples, the pharmaceutical composition comprises an active agent consisting essentially of the polymorphic or amorphous form of the anhydrate, hydrate, or solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide. In some examples, including any of the foregoing examples, the method is a method of treating or suppressing an oxidative stress disorder. In some examples, including any of the foregoing examples, the method is a method of treating an oxidative stress disorder. In some examples, including any of the foregoing examples, the method is a method of suppressing an oxidative stress disorder. In some examples, including any of the foregoing examples, the oxidative stress disorder is selected from the group consisting of: a mitochondrial disorder; an inherited mitochondrial disease; Alpers Disease; Barth syndrome; a Beta-oxidation Defect; Carnitine-Acyl-Carnitine Deficiency; Carnitine Deficiency; a Creatine Deficiency Syndrome; Co-Enzyme Q10 Deficiency; Complex I Deficiency; Complex II Deficiency; Complex III Deficiency; Complex IV Deficiency; Complex V Deficiency; COX Deficiency; chronic progressive external ophthalmoplegia (CPEO); CPT I Deficiency; CPT II Deficiency; Friedreich's Ataxia (FA); Glutaric Aciduria Type II; Kearns-Sayre Syndrome (KSS); Lactic Acidosis; Long-Chain Acyl-CoA Dehydrogenase Deficiency (LCAD); LCHAD; Leigh's syndrome; Leigh-like Syndrome; Leber's Hereditary Optic Neuropathy (LHON); Lethal Infantile Cardiomyopathy (LIC); Luft Disease; Multiple Acyl-CoA Dehydrogenase Deficiency (MAD); Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCAD); Mitochondrial Myopathy, Encephalopathy, Lactacidosis, Stroke (MELAS); Myoclonic Epilepsy with Ragged Red Fibers (MERRF); Mitochondrial Recessive Ataxia Syndrome (MIRAS); Mitochondrial Cytopathy, Mitochondrial DNA Depletion; Mitochondrial Encephalopathy; Mitochondrial Myopathy; Myoneurogastrointestina Disorder and Encephalopathy (MNGIE); Neuropathy, Ataxia, and Retinitis Pigmentosa (NARP); Pearson Syndrome; Pyruvate Carboxylase Deficiency; Pyruvate Dehydrogenase Deficiency; a

POLG Mutation; a Respiratory Chain Disorder; Short-Chain Acyl-CoA Dehydrogenase Deficiency (SCAD); SCHAD; Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD); a myopathy; cardiomyopathy; encephalomyopathy; a neurodegenerative disease; Parkinson's disease; Alzheimer's disease; amyotrophic lateral sclerosis (ALS); a motor neuron disease; a neurological disease; epilepsy; an age-associated disease; macular degeneration; diabetes; metabolic syndrome; cancer; brain cancer; a genetic disease; Huntington's Disease; a mood disorder; schizophrenia; bipolar disorder; a pervasive developmental disorder; autistic disorder; Asperger's syndrome; childhood disintegrative disorder (CDD); Rett's disorder; PDD-not otherwise specified (PDD-NOS); a cerebrovascular accident; stroke; a vision impairment; optic neuropathy; dominant inherited juvenile optic atrophy; optic neuropathy caused by a toxic agent; glaucoma; Stargardt's macular dystrophy; diabetic retinopathy; diabetic maculopathy; retinopathy of prematurity; ischemic reperfusion-related retinal injury; oxygen poisoning; a haemoglobinopathy; thalassemia; sickle cell anemia; seizures; ischemia; renal tubular acidosis; attention deficit/hyperactivity disorder (ADHD); a neurodegenerative disorder resulting in hearing or balance impairment; Dominant Optic Atrophy (DOA); Maternally inherited diabetes and deafness (MIDD); chronic fatigue; contrast-induced kidney damage; contrast-induced retinopathy damage; Abetalipoproteinemia; retinitis pigmentosum; Wolfram's disease; Tourette syndrome; cobalamin c defect; methylmalonic aciduria; glioblastoma; Down's syndrome; acute tubular necrosis; a muscular dystrophy; a leukodystrophy; Progressive Supranuclear Palsy; spinal muscular atrophy; hearing loss; noise induced hearing loss; traumatic brain injury; Juvenile Huntington's Disease; Multiple Sclerosis; NGLY1; Multiple System Atrophy; Adrenoleukodystrophy; and Adrenomyeloneuropathy. In some examples, the oxidative stress disorder is Multiple System Atrophy. In some examples, including any of the foregoing examples, the oxidative stress disorder is cancer. In some examples, including any of the foregoing examples, the oxidative stress disorder is bipolar disorder. In some examples, the oxidative stress disorder is schizophrenia. In some examples, including any of the foregoing examples, the oxidative stress disorder is an age-associated disease. In some examples, including any of the foregoing examples, the oxidative stress disorder is Huntington's Disease. In some examples, including any of the foregoing examples, the oxidative stress disorder is Alzheimer's disease. In some examples, including any of the foregoing examples, the oxidative stress disorder is amyotrophic lateral sclerosis (ALS). In some examples, including any of the foregoing examples, the oxidative stress disorder is

epilepsy. In some examples, including any of the foregoing examples, the oxidative stress disorder is Parkinson's disease. In some examples, including any of the foregoing examples, the oxidative stress disorder is seizures. In some examples, including any of the foregoing examples, the oxidative stress disorder is stroke. In some examples, including any of the foregoing examples, the oxidative stress disorder is a mitochondrial disorder. In some examples, including any of the foregoing examples, the oxidative stress disorder is an inherited mitochondrial disease. In some examples, including any of the foregoing examples, the oxidative stress disorder is Friedreich's Ataxia (FA). In some examples, including any of the foregoing examples, the oxidative stress disorder is Kearns-Sayre Syndrome (KSS). In some examples, including any of the foregoing examples, the oxidative stress disorder is Leigh Syndrome or Leigh-like Syndrome. In some examples, including any of the foregoing examples, the oxidative stress disorder is Leber's Hereditary Optic Neuropathy (LHON). In some examples, including any of the foregoing examples, the oxidative stress disorder is Mitochondrial Myopathy, Encephalopathy, Lactacidosis, Stroke (MELAS). In some examples, including any of the foregoing examples, the oxidative stress disorder is Myoclonic Epilepsy with Ragged Red Fibers (MERRF). In some examples, including any of the foregoing examples, the oxidative stress disorder is macular degeneration. In some examples, including any of the foregoing examples, the oxidative stress disorder is brain cancer. In some examples, including any of the foregoing examples, the oxidative stress disorder is autistic disorder. In some examples, including any of the foregoing examples, the oxidative stress disorder is Rett's disorder. In some examples, including any of the foregoing examples, the oxidative stress disorder is Maternally inherited diabetes and deafness (MIDD). In some examples, including any of the foregoing examples, the oxidative stress disorder is chronic fatigue. In some examples, including any of the foregoing examples, the oxidative stress disorder is contrast-induced kidney damage. In some examples, including any of the foregoing examples, the oxidative stress disorder is contrast-induced retinopathy damage. In some examples, including any of the foregoing examples, the oxidative stress disorder is cobalamin c defect. In some examples, including any of the foregoing examples, the method is a method for modulating one or more energy biomarkers, normalizing one or more energy biomarkers, or enhancing one or more energy biomarkers, wherein the one or more energy biomarkers are selected from the group consisting of: lactic

acid (lactate) levels, either in whole blood, plasma, cerebrospinal fluid, or cerebral ventricular fluid; pyruvic acid (pyruvate) levels, either in whole blood, plasma, cerebrospinal fluid, or cerebral ventricular fluid; lactate/pyruvate ratios, either in whole blood, plasma, cerebrospinal fluid, or cerebral ventricular fluid; total, reduced or oxidized glutathione levels, or reduced/oxidized glutathione ratio either in whole blood, plasma, lymphocytes, cerebrospinal fluid, or cerebral ventricular fluid; total, reduced or oxidized cysteine levels, or reduced/oxidized cysteine ratio either in whole blood, plasma, lymphocytes, cerebrospinal fluid, or cerebral ventricular fluid; phosphocreatine levels, NADH (NADH +H+) levels; NADPH (NADPH+H+) levels; NAD levels; NADP levels; ATP levels; reduced coenzyme Q (CoQ_{red}) levels; oxidized coenzyme Q (CoQ_{ox}) levels; total coenzyme Q (CoQ_{tot}) levels; oxidized cytochrome C levels; reduced cytochrome C levels; oxidized cytochrome C/reduced cytochrome C ratio; acetoacetate levels, β hydroxy butyrate levels, acetoacetate/β hydroxy butyrate ratio, 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels; levels of reactive oxygen species; levels of oxygen consumption (VO2); levels of carbon dioxide output (VCO2); respiratory quotient (VCO2/VO2); exercise tolerance; and anaerobic threshold. Energy biomarkers can be measured in whole blood, plasma, cerebrospinal fluid, cerebroventricular fluid, arterial blood, venous blood, or any other body fluid, body gas, or other biological sample useful for such measurement. In some examples, including any of the foregoing examples, the levels are modulated to a value within about 2 standard deviations of the value in a healthy subject. In some examples, including any of the foregoing examples, the levels are modulated to a value within about 1 standard deviation of the value in a healthy subject. In some examples, including any of the foregoing examples, the levels in a subject are changed by at least about 10% above or below the level in the subject prior to modulation. In some examples, including any of the foregoing examples, the levels are changed by at least about 20% above or below the level in the subject prior to modulation. In some examples, including any of the foregoing examples, the levels are changed by at least about 30% above or below the level in the subject prior to modulation. In some examples, including any of the foregoing examples, the levels are changed by at least about 40% above or below the level in the subject prior to modulation. In some examples, including any of the foregoing examples, the levels are changed by at least about 50% above or below the level in the subject prior to modulation. In some examples, including any of the foregoing examples, the levels are changed by at least about 75% above or below the level in the

subject prior to modulation. In some examples, including any of the foregoing examples, the levels are changed by at least about 100% above or at least about 90% below the level in the subject prior to modulation. In some examples, including any of the foregoing examples, the subject or subjects in which a method of treating or suppressing an oxidative stress disorder, modulating one or more energy biomarkers, normalizing one or more energy biomarkers, or enhancing one or more energy biomarkers is performed is/are selected from the group consisting of subjects undergoing strenuous or prolonged physical activity; subjects with chronic energy problems; subjects with chronic respiratory problems; pregnant females; pregnant females in labor; neonates; premature neonates; subjects exposed to extreme environments; subjects exposed to hot environments; subjects exposed to cold environments; subjects exposed to environments with lower-than-average oxygen content; subjects exposed to environments with higher-than-average carbon dioxide content; subjects exposed to environments with higher-than-average levels of air pollution; airline travelers; flight attendants; subjects at elevated altitudes; subjects living in cities with lower-than-average air quality; subjects working in enclosed environments where air quality is degraded; subjects with lung diseases; subjects with lower-than-average lung capacity; tubercular patients; lung cancer patients; emphysema patients; cystic fibrosis patients; subjects recovering from surgery; subjects recovering from illness; elderly subjects; elderly subjects experiencing decreased energy; subjects suffering from chronic fatigue; subjects suffering from chronic fatigue syndrome; subjects undergoing acute trauma; subjects in shock; subjects requiring acute oxygen administration; subjects requiring chronic oxygen administration; subjects requiring organ visualization via contrast solution; or other subjects with acute, chronic, or ongoing energy demands who can benefit from enhancement of energy biomarkers.

[0045] The disclosure also provides use of a polymorphic or amorphous form of an anhydrate, a hydrate, or a solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide as described herein, including any of the foregoing or hereafter described examples, for treating or suppressing an oxidative stress disorder. In another aspect of the disclosure is use of a therapeutically effective amount of the polymorph as defined herein, the composition as defined herein, or the pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment or suppression of an oxidative stress disorder. In some examples, the form is polymorph Form I. In some examples, the form is polymorph Form II. In some examples, the form is polymorph Form III. In some examples, the form is polymorph Form IV. In some examples, the form is polymorph Form V. In some examples, the form is polymorph Form VI. In some examples, the form is amorphous. The disclosure also provides use of a polymorphic or amorphous

form of an anhydrate, a hydrate, or a solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide as described herein, including any of the foregoing or hereafter described examples, in the manufacture of a medicament for use in treating or suppressing an oxidative stress disorder. In some examples, the form is polymorph Form I. In some examples, the form is polymorph Form II. In some examples, the form is polymorph Form III. In some examples, the form is polymorph Form IV. In some examples, the form is polymorph Form V. In some examples, the form is polymorph Form VI. In some examples, the form is amorphous.

[0046] For all compositions described herein, and all methods using a composition described herein, the compositions can either comprise the listed components or steps, or can "consist essentially of" the listed components or steps. When a composition is described as "consisting essentially of" the listed components, the composition contains the components listed, and may contain other components which do not substantially affect the condition being treated, but do not contain any other components which substantially affect the condition being treated other than those components expressly listed; or, if the composition does contain extra components other than those listed which substantially affect the condition being treated, the composition does not contain a sufficient concentration or amount of the extra components to substantially affect the condition being treated. When a method is described as "consisting essentially of" the listed steps, the method contains the steps listed, and may contain other steps that do not substantially affect the condition being treated, but the method does not contain any other steps which substantially affect the condition being treated other than those steps expressly listed. As a non-limiting specific example, when a composition is described as 'consisting essentially of' a component, the composition may additionally contain any amount of pharmaceutically acceptable carriers, vehicles, or diluents and other such components which do not substantially affect the condition being treated.

[0047] The disclosure also provides a process for the preparation of polymorph Form I of an anhydrate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, wherein the process comprises the steps: (a) contacting (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide with a liquid comprising IPA; and (b) removing the liquid. In some examples, step (a) comprises dissolving the (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide in the liquid. In some examples, step (a) comprises slurrying the (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-

3,6-dioxocyclohexa-1,4-dienyl)butanamide in the liquid. In some examples, the slurrying in step (a) may be performed for at least about 24 hours. In some examples, including any of the foregoing examples, the liquid is 100% IPA In some examples, including any of the foregoing examples, the liquid is 98% IPA/2% water (v/v). In some examples, including any of the foregoing examples, the process further comprises step (a)(i): adding heptane to the liquid. In some examples, including any of the foregoing examples, step (b) comprises filtering the (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide. In some examples, including any of the foregoing examples, the mixture in step (a) or step (a)(i) may be seeded with Form I crystals. In some examples, including any of the foregoing examples, the (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide in step (a) is at least about 95% pure. In various examples, including any of the foregoing examples, the (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide in step (a) is at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 99.5%, at least about 99.9% pure. The disclosure also provides an anhydrate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide prepared by the above described process.

[0048] The disclosure also provides a process for the preparation of polymorph Form II of an anhydrate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, wherein the process comprises the steps: (a) dissolving the (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide in EtOAc, (b) rapidly cooling the mixture from (a), and (c) isolating the (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide. In some examples, the initial (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide is Form I. In some examples, including any of the foregoing examples, step (a) is at about 60°C. In some examples, including any of the foregoing examples, step (b) comprises rapidly cooling the mixture in an ice bath. In some examples, including any of the foregoing examples, the mixture in step (b) may be seeded with Form II crystals. The disclosure also provides an anhydrate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide prepared by the above described process.

[0049] The disclosure also provides a process for the preparation of polymorph Form III of a solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-

dienyl)butanamide, wherein the process comprises the steps: (a) combining (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide and 0.5% MC/2%Tween 80 in water to create a slurry; (b) slurrying the mixture from (a), and (c) removing the 0.5% MC/2%Tween 80 in water. As used herein "MC" refers to methyl cellulose and "Tween 80" refers to a commercially available polysorbate nonionic surfactant In some examples, the initial (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide is Form I. In some examples, including any of the foregoing examples, step (b) is performed for at least about 24 hours. In some examples, including any of the foregoing examples, step (b) is at room temperature. In some examples, including any of the foregoing examples, the mixture in step (b) may be seeded with Form III crystals. The disclosure also provides a solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide prepared by the above described process.

[0050] The disclosure also provides a process for the preparation of polymorph Form III of a solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, wherein the process comprises the steps: (a) combining (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide and 0.5% MC in water to create a slurry; (b) slurrying the mixture from (a), and (c) removing the 0.5% MC in water. In some examples, the initial (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide is Form I, II, IV, V or VI. In some examples, including any of the foregoing examples, step (b) is performed at room temperature. In some examples, including any of the foregoing examples, step (b) may be performed for at least about 7 days. In some examples, including any of the foregoing examples, the mixture in step (b) may be seeded with Form III crystals. The disclosure also provides a solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide prepared by the above described process.

BRIEF DESCRIPTION OF THE FIGURES

[0051] Figure 1 shows a XRPD stack plot of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide short term slurry experiments, a) Pattern C, from slurry in 0.5% Methyl Cellulose/2% Tween 80, b) Pattern B, from slurry in tetrahydrofuran (THF), and c) starting material, Pattern A.

CLAIMS

What is claimed is:

1. An polymorph of an anhydrate, a hydrate, or a solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, wherein the polymorph is selected from the group consisting of Forms II and III;

wherein a powder X-ray diffraction pattern for polymorph Form II comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.63, 10.85, 11.33, and 19.33;

wherein a powder X-ray diffraction pattern for polymorph Form III comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.16, 14.02, 15.23, and 21.10; and

wherein the XRPD pattern is generated at 25 °C.

2. The polymorph of claim 1, wherein the polymorph is Form III, wherein a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.16, 14.02, 15.23, 21.10, and 22.69.

3. The polymorph of claim 1, wherein the polymorph is Form III, having a DSC thermogram comprising three endothermic peaks at about 72.0 and 150.7 °C.

4. A composition comprising the polymorph of any one of claims 2-3, wherein the composition is essentially free of Forms I, II, IV, V, and VI,

wherein a powder X-ray diffraction pattern for polymorph Form I comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 12.06, 15.33 17.03, and 17.26;

wherein a powder X-ray diffraction pattern for polymorph Form II comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.63, 10.85, 11.33, and 19.33;

wherein a powder X-ray diffraction pattern for polymorph Form IV comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 8.76, 12.97, 13.20, and 16.66;

wherein a powder X-ray diffraction pattern for polymorph Form V comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.61, 11.49, 12.93, and 15.45; and

wherein a powder X-ray diffraction pattern for polymorph Form VI comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 6.27, 9.91, 12.94, and 15.71.

5. A composition comprising the polymorph of any one of claims 2-3, wherein at least about 95% by mole of the composition is the polymorph Form III, exclusive of any solvents, carriers or excipients.

6. The polymorph of claim 1, wherein the polymorph is Form II, a solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, wherein a powder X-ray diffraction pattern for the polymorph comprises characteristic peaks at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.63, 10.85, 11.33, 13.47, and 19.33.

7. The polymorph of claim 1, wherein the polymorph is Form II, having a DSC thermogram comprises two endothermic peaks at about 133.9 and 151.3°C.

8. A composition comprising the polymorph of any one of claims 6-7, wherein the composition is essentially free of Forms I, III-VI,

wherein a powder X-ray diffraction pattern for polymorph Form I comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 12.06, 15.33 17.03, and 17.26;

wherein a powder X-ray diffraction pattern for polymorph Form III comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.16, 14.02, 15.23, and 21.10;

wherein a powder X-ray diffraction pattern for polymorph Form IV comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 8.76, 12.97, 13.20, and 16.66;

wherein a powder X-ray diffraction pattern for polymorph Form V comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 9.61, 11.49, 12.93, and 15.45; and

wherein a powder X-ray diffraction pattern for polymorph Form VI comprises characteristic peaks at least at the following angular positions, wherein the angular positions may vary by ± 0.2: 6.27, 9.91, 12.94, and 15.71.

9. A composition comprising the polymorph of any one of claims 6-7, wherein at least about 95% by mole of the composition is the polymorph Form II, exclusive of any solvents, carriers or excipients.

10. A pharmaceutical composition comprising the polymorph of any one of claims 1-3, 6, and 7, or the composition of any one of claims 4, 5, 8, and 9, and a pharmaceutically acceptable carrier.

11. The pharmaceutical composition of claim 10, wherein the pharmaceutical composition has an HPLC purity of more than about 95% for the anhydrate, hydrate, or solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, exclusive of any solvents, carriers or excipients.

12. The pharmaceutical composition of claim 10, wherein the pharmaceutical composition has an HPLC purity of more than about 99% for the anhydrate, hydrate, or solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, exclusive of any solvents, carriers or excipients.

13. The pharmaceutical composition of claim 11, wherein the pharmaceutical composition has an HPLC purity of more than about 99.9% for the anhydrate, hydrate, or solvate of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide, exclusive of any solvents, carriers or excipients.

14. Use of a therapeutically effective amount of the polymorph of any one of claims 1-3, 6, and 7, the composition of any one of claims 4, 5, 8, and 9, or the pharmaceutical composition of any one of claims 10-13 in the manufacture of a medicament for the treatment or suppression of an oxidative stress disorder.

15. The use of claim 14, wherein the oxidative stress disorder is selected from the group consisting of: a mitochondrial disorder; an inherited mitochondrial disease; Alpers Disease; Barth syndrome; a Beta-oxidation Defect; Carnitine-Acyl-Carnitine Deficiency; Carnitine Deficiency; a Creatine Deficiency Syndrome; Co-Enzyme Q10 Deficiency; Complex I Deficiency; Complex II Deficiency; Complex III Deficiency; Complex IV Deficiency; Complex V Deficiency; COX Deficiency; chronic progressive external ophthalmoplegia (CPEO); CPT I Deficiency; CPT II Deficiency; Friedreich's Ataxia (FA); Glutaric Aciduria Type II; Kearns-Sayre Syndrome (KSS); Lactic Acidosis; Long-Chain Acyl-CoA Dehydrogenase Deficiency (LCAD); LCHAD; Leigh Syndrome; Leigh-like Syndrome; Leber's Hereditary Optic Neuropathy (LHON); Lethal Infantile Cardiomyopathy (LIC); Luft Disease; Multiple Acyl-CoA Dehydrogenase Deficiency (MAD); Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCAD); Mitochondrial Myopathy, Encephalopathy, Lactacidosis, Stroke (MELAS); Myoclonic Epilepsy with Ragged Red Fibers (MERRF); Mitochondrial Recessive Ataxia Syndrome (MIRAS); Mitochondrial Cytopathy, Mitochondrial DNA Depletion; Mitochondrial Encephalopathy; Mitochondrial Myopathy; Myoneurogastrointestinal Disorder and Encephalopathy (MNGIE); Neuropathy, Ataxia, and Retinitis Pigmentosa (NARP); Pearson Syndrome; Pyruvate Carboxylase Deficiency; Pyruvate Dehydrogenase Deficiency; a Respiratory Chain Disorder; Short-Chain Acyl-CoA Dehydrogenase Deficiency (SCAD); SCHAD; Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD); a myopathy; cardiomyopathy; encephalomyopathy; a neurodegenerative disease; Parkinson's disease; Alzheimer's disease; amyotrophic lateral sclerosis (ALS); a motor neuron disease; a neurological disease; epilepsy; an age-associated disease; macular degeneration; diabetes; metabolic syndrome; cancer; brain cancer; a genetic disease; Huntington's Disease; a mood disorder; schizophrenia; bipolar disorder; a pervasive developmental disorder; autistic disorder; Asperger's syndrome; childhood disintegrative disorder (CDD); Rett's disorder; PDD-not otherwise specified (PDD-NOS); a cerebrovascular accident; stroke; a vision impairment; optic

neuropathy; dominant inherited juvenile optic atrophy; optic neuropathy caused by a toxic agent; glaucoma; Stargardt's macular dystrophy; diabetic retinopathy; diabetic maculopathy; retinopathy of prematurity; ischemic reperfusion-related retinal injury; oxygen poisoning; a haemoglobinopathy; thalassemia; sickle cell anemia; seizures; ischemia; renal tubular acidosis; attention deficit/hyperactivity disorder (ADHD); a neurodegenerative disorder resulting in hearing or balance impairment; Dominant Optic Atrophy (DOA); Maternally inherited diabetes and deafness (MIDD); chronic fatigue; contrast-induced kidney damage; contrast-induced retinopathy damage; Abetalipoproteinemia; retinitis pigmentosum; Wolfram's disease; Tourette syndrome; cobalamin c defect; methylmalonic aciduria; glioblastoma; Down's syndrome; acute tubular necrosis; a muscular dystrophy; a leukodystrophy; Progressive Supranuclear Palsy; spinal muscular atrophy; hearing loss; noise induced hearing loss; traumatic brain injury; Juvenile Huntington's Disease; Multiple Sclerosis; NGLY1; Multiple System Atrophy; Adrenoleukodystrophy; and Adrenomyeloneuropathy.

16. The use of claim 15, wherein the oxidative stress disorder is Huntington's Disease.

17. The use of claim 15, wherein the oxidative stress disorder is amyotrophic lateral sclerosis (ALS).

18. The use of claim 15, wherein the oxidative stress disorder is Parkinson's disease.

19. The use of claim 15, wherein the oxidative stress disorder is Multiple Sclerosis.