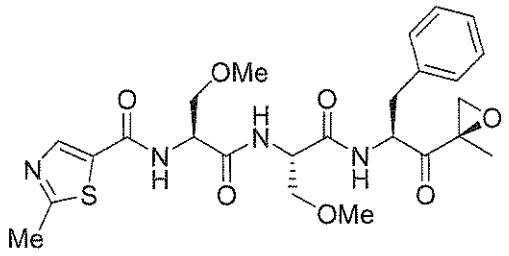
amidotransferase (GAT), and bacterial glycosylasparaginase. In addition to the ubiquitously expressed β subunits, higher vertebrates also possess three interferon-γ-inducible β subunits (LMP7, LMP2 and MECLl), which replace their normal counterparts, $ß_5$, $ß_1$ and $ß_7$ respectively, thus altering the catalytic activities of the proteasome. Through the use of different peptide substrates, three major proteolytic activities have been defined for the eukaryote 20S proteasome: chymotrypsin-like activity (CT-L), which cleaves after large hydrophobic residues; trypsin-like activity (T-L), which cleaves after basic residues; and peptidylglutamyl peptide hydrolyzing activity (PGPH), which cleaves after acidic residues. Two additional less characterized activities have also been ascribed to the proteasome: BrAAP activity, which cleaves after branched-chain amino acids; and SNAAP activity, which cleaves after small neutral amino acids. The major proteasome proteolytic activities appear to be contributed by different catalytic sites, since inhibitors, point mutations in β subunits and the exchange of γ interferon-inducing β subunits alter these activities to various degrees.

Improved compositions and methods for preparing and formulating proteasome inhibitor(s) are needed.

Summary ~~of the Invention~~

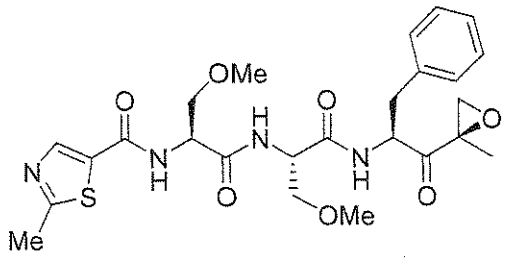
In a first aspect, there is provided a method for preparing a crystalline compound of Formula (II)



(II)

comprising (i) preparing a solution of a compound of Formula (II) in an organic solvent; (ii) bringing the solution to supersaturation to cause formation of crystals; and (iii) isolating the crystals, wherein bringing the solution to supersaturation comprises addition of an anti-solvent, allowing the solution to cool, reducing the volume of the solution, or any combination thereof, and wherein the crystalline compound has 2θ values 8.94; 9.39; 9.76; 10.60; 11.09; 12.74; 15.27; 17.74; 18.96; 20.58; 20.88; 21.58; 21.78; 22.25; 22.80; 24.25; 24.66; 26.04; 26.44; 28.32; 28.96; 29.65; 30.22; 30.46; 30.78; 32.17; 33.65; 34.49; 35.08; 35.33; 37.85; 38.48.

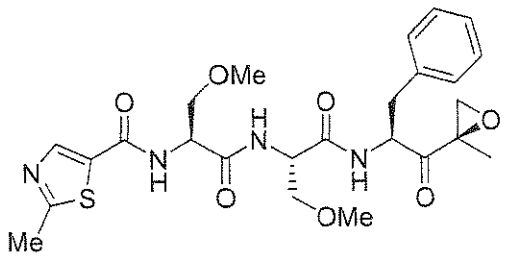
In a second aspect, there is provided a crystalline compound having a structure of Formula (II),



(II)

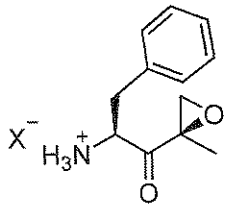
wherein the crystalline compound of Formula (II) has 2θ values 8.94; 9.39; 9.76; 10.60; 11.09; 12.74; 15.27; 17.74; 18.96; 20.58; 20.88; 21.58; 21.78; 22.25; 22.80; 24.25; 24.66; 26.04; 26.44; 28.32; 28.96; 29.65; 30.22; 30.46; 30.78; 32.17; 33.65; 34.49; 35.08; 35.33; 37.85; 38.48.

In a third aspect, there is provided a method for the preparation of a crystalline compound of Formula (II),



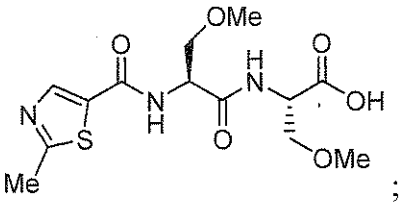
(II)

comprising (i) reacting a compound of Formula (III)



(III)

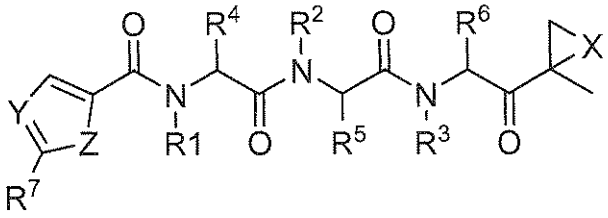
wherein X is any suitable counterion, with a compound of Formula (IV) in a second organic solvent



(IV)

(ii) preparing a solution of a compound of Formula (II) in the second organic solvent; (iii) bringing the solution to supersaturation to permit formation of crystals; and (iv) isolating the crystals to provide a crystalline compound of Formula (II), wherein bringing the solution to supersaturation comprises addition of an anti-solvent, allowing the solution to cool, reducing the volume of the solution, or any combination thereof, and wherein the crystalline compound of Formula (II) has 2θ values 8.94; 9.39; 9.76; 10.60; 11.09; 12.74; 15.27; 17.74; 18.96; 20.58; 20.88; 21.58; 21.78; 22.25; 22.80; 24.25; 24.66; 26.04; 26.44; 28.32; 28.96; 29.65; 30.22; 30.46; 30.78; 32.17; 33.65; 34.49; 35.08; 35.33; 37.85; 38.48.

Also disclosed are~~One aspect of the invention relates to~~ crystalline compounds having a structure of Formula (I) or a pharmaceutically acceptable salt thereof,



I

wherein

X is O, NH, or N-alkyl, preferably O;

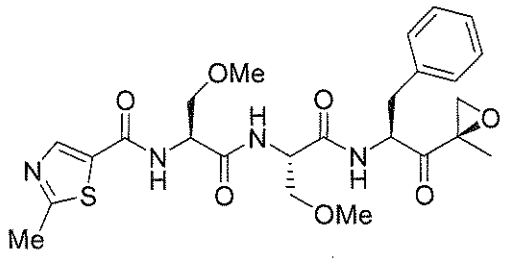
Y is N, , S, or $C(R^8)_2$, preferably NH;

Z is NH, N-alkyl, O, S or $C(R^8)_2$, preferably S;

R^1, R^2, and R^3 are hydrogen;

We Claim:

1. A method for preparing a crystalline compound of Formula (II)



(II)

comprising (i) preparing a solution of a compound of Formula (II) in an organic solvent; (ii) bringing the solution to supersaturation to cause formation of crystals; and (iii) isolating the crystals-, wherein bringing the solution to supersaturation comprises addition of an anti-solvent, allowing the solution to cool, reducing the volume of the solution, or any combination thereof, and wherein the crystalline compound has 2θ values 8.94; 9.39; 9.76; 10.60; 11.09; 12.74; 15.27; 17.74; 18.96; 20.58; 20.88; 21.58; 21.78; 22.25; 22.80; 24.25; 24.66; 26.04; 26.44; 28.32; 28.96; 29.65; 30.22; 30.46; 30.78; 32.17; 33.65; 34.49; 35.08; 35.33; 37.85; 38.48.

2. A method of claim 1, wherein the organic solvent is selected from acetonitrile, ethyl acetate, heptanes, hexanes, isopropyl acetate, methanol, methylethyl ketone, tetrahydrofuran, and toluene, or any combination thereof.

3. A method of claim 2, wherein the organic solvent is selected from acetonitrile, heptanes, hexanes, methanol, tetrahydrofuran, and toluene.

4. A method of claim 3, wherein the organic solvent is selected from hexanes, tetrahydrofuran and toluene.

5. A method of claim 1, wherein bringing the solution to supersaturation comprises adding an anti-solvent, cooling the solution to ambient temperature, and reducing the volume of the solution.

6. A method of claim 1, wherein the anti-solvent is added slowly.

7. A method of claim 1, wherein the anti-solvent is selected from hexanes, toluene and water.

8. A method of claim 1, wherein the volume reduction is performed by evaporation.

9. A method of any one of claims 1 to 8, further comprising seeding the solution.

10. A method of claim 9, further comprising washing the crystals.

11. A method of claim 10, wherein the washing comprises washing with a liquid selected from anti-solvent, acetonitrile, heptanes, hexanes, methanol, tetrahydrofuran, toluene, water, or a combination thereof.

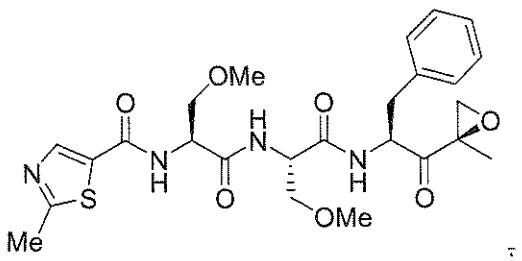
12. A method of claim 11, wherein washing comprises washing with a combination of an anti-solvent and the organic solvent.

13. A method of claim 12, wherein the anti-solvent is hexanes or heptanes.

14. A method of any one of claims 1 to 13, wherein isolating the crystals comprises filtering the crystals.

15. A method of any one of claims 1 to 14, further comprising drying the crystals under reduced pressure.

16. A crystalline compound having a structure of Formula (II),



(II)

wherein the crystalline compound of Formula (II) has 2θ values 8.94; 9.39; 9.76; 10.60; 11.09; 12.74; 15.27; 17.74; 18.96; 20.58; 20.88; 21.58; 21.78; 22.25; 22.80; 24.25; 24.66; 26.04; 26.44; 28.32; 28.96; 29.65; 30.22; 30.46; 30.78; 32.17; 33.65; 34.49; 35.08; 35.33; 37.85; 38.48.