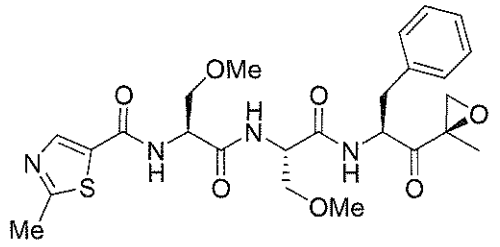
amidotransferase (GAT), and bacterial glycosylasparaginase. In addition to the ubiquitously expressed β subunits, higher vertebrates also possess three interferon-γ-inducible β subunits (LMP7, LMP2 and MECL1), which replace their normal counterparts, $ß_5$, $ß_1$ and $ß_7$ respectively, thus altering 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~~

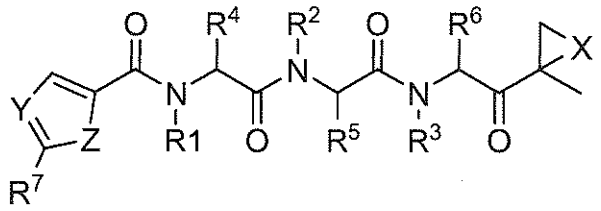
In one aspect, there is provided a pharmaceutical composition comprising (a) a pharmaceutically acceptable carrier and (b) a crystalline compound having a structure of Formula (II)



(II)

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; and 38.48.

One ~~aspect~~embodiment of the ~~invention~~disclosure 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;

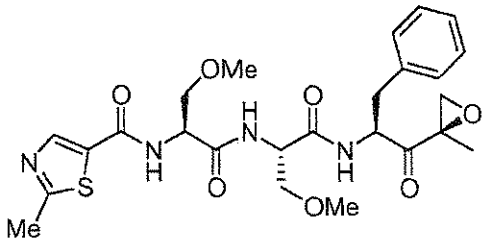
Y is N, , S, or $C(R^8)_2$, preferably NH;

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.

2. A method of claim 1, wherein the organic solvent is selected from acetonitrile, ethyl acetate, heptanes, hexanes, isopropyl acetate, methanol, methylethyl ketone, tetrahydrofuran, toluene and water, 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 any one of claims 1 to 4, 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.

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

7. A method of claim 5, wherein the anti-solvent is added slowly.

8. A method of claim 5, wherein the anti-solvent is selected from hexanes, toluene and water.

9. A method of claim 5, wherein the volume reduction is performed by evaporation.

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

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

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

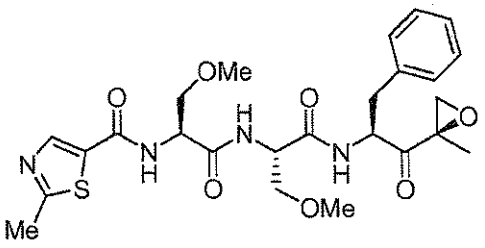
13. A method of claim 12, wherein washing comprises washing with a combination of an anti-solvent and the organic solvent.

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

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

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

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



(II)

18. A crystalline compound of claim 17, having a DSC thermogram substantially as shown in Figure 1.

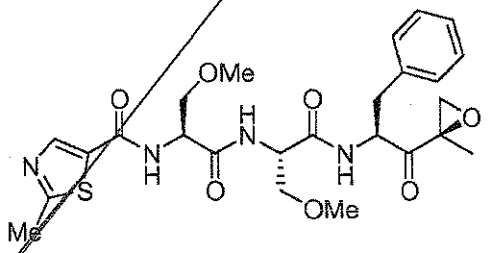
19. A crystalline compound of claim 17, having a melting point of about 140 to about 155 °C.

20. A crystalline compound of claim 19, having a melting point of about 145 to about 150 °C.

21. A crystalline compound of claim 17, having an XRPD pattern substantially as shown in Figure 2.

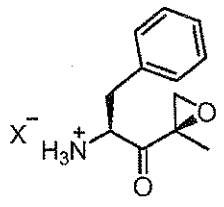
22. A crystalline compound of claim 17 having 2θ values 8.94; 9.39; 9.76; 10.60; 11.09; 12.74; 15.27; 17.74; 18.96; 20.58; 20.88; 21.58; 21.78; 22.25; 22.80; 24.25; 24.66; 26.04; 26.44; 28.32; 28.96; 29.65; 30.22; 30.46; 30.78; 32.17; 33.65; 34.49; 35.08; 35.33; 37.85; 38.48.

23. A method for the preparation of a crystalline compound of Formula (II),



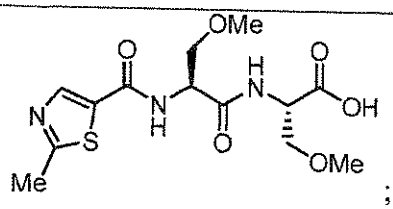
(II)

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



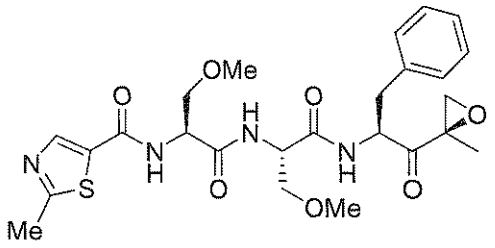
;

(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).

Claims

1. A pharmaceutical composition comprising (a) a pharmaceutically acceptable carrier and (b) a crystalline compound having a structure of Formula (II)



(II)

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; and 38.48.

2. The pharmaceutical composition of claim 1 in a dosage amount ranging from about 0.01 mg/kg to about 50 mg/kg by weight of the subject to whom the composition is administered.

3. The pharmaceutical composition of claim 1 or 2, wherein the composition is an orally administrable composition.

4. The pharmaceutical composition of claim 3, wherein the orally administrable composition is selected from the group consisting of a tablet, a capsule, a granule, a powder and a syrup.

5. The pharmaceutical composition of any one of claims 1 to 4, wherein the crystalline compound exhibits a differential scanning calorimetry (DSC) thermogram characterized with an endothermic peak at 147°C.

6. The pharmaceutical composition of claim 1 for treatment of cancer.

7. The pharmaceutical composition of claim 6, wherein the cancer is a cancer of the bladder, blood, bone, brain, breast, cervix, chest, colon, endometrium, esophagus, eye, head, kidney, liver, lung, lymph nodes, mouth, neck, ovaries, pancreas, prostate, rectum, renal, skin, stomach, testis, throat or uterus.

8. The pharmaceutical composition of claim 1 for treatment of leukemia, acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), hairy cell leukemia, small lymphocytic lymphoma, lymphoplasmacytic lymphoma, plasma cell myeloma, plasmcytoma or multiple myeloma.

9. The pharmaceutical composition of claim 1 for treatment of leukemia, acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL) or chronic myelogenous leukemia (CML).

10. The pharmaceutical composition of claim 1 for treatment of multiple myeloma.

11. The pharmaceutical composition of claim 1 for treatment of Waldenstrom's macroglobulinemia.

12. The pharmaceutical composition of claim 1 for treatment of a cancer selected from hematological cancers, Waldenstrom's macroglobulinemia, multiple myeloma, diffuse B cell lymphoma, mantle cell lymphoma, pancreatic cancer and lung cancer.

13. The pharmaceutical composition of claim 1 wherein the crystalline compound Formula (II) exhibits from 0.0 to 0.3% weight loss in the temperature range of 25°C to 125°C in a thermogravimetric analysis.

14. The pharmaceutical composition of claim 1 or 13 for treatment of myodisplastic syndrome or myeloproliferative disease.

15. The pharmaceutical composition of claim 1 or 2, wherein the composition is a parenterally administrable composition.

16. The pharmaceutical composition of claim 3 or 4, wherein the orally administrable composition is a tablet.

17. The pharmaceutical composition of claim 3 or 4, wherein the orally administrable composition is a capsule.

18. The pharmaceutical composition of claim 3 or 4, wherein the orally administrable composition is a granule.

19. The pharmaceutical composition of claim 3 or 4, wherein the orally administrable composition is a powder.