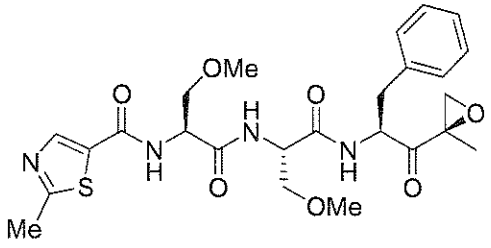
amidotransferase (GAT), and bacterial glycosylasparaginase. In addition to the ubiquitously expressed β subunits, higher vertebrates also possess three interferon-γ-inducible β subunits (LMP7, LMP2 and MECL1), which replace their normal counterparts, $ß_5$, $ß_1$ and $ß_7$ respectively, thus altering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

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)

In one aspect, there is provided the pharmaceutical composition as described herein for use in treating cancer.

In one aspect, there is provided the pharmaceutical composition as described herein for use in treating 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.

In one aspect, there is provided the pharmaceutical composition as described herein for use in treating multiple myeloma.

In one aspect, there is provided the pharmaceutical composition as described herein for use in treating Waldenstrom's macroglobulinemia.

In one aspect, there is provided the pharmaceutical composition as described herein for use in treating a cancer selected from hematological cancers, Waldenstrom's macroglobulinemia, multiple lyeloma, diffuse B cell lymphoma, mantle cell lymphoma, pancreatic cancer and lung cancer.

In one aspect, there is provided the pharmaceutical composition as described herein for use in treating myodisplastic syndrome or myeloproliferative disease.

In one aspect, there is provided the pharmaceutical composition as described herein for use in treating an autoimmune disease.

In one aspect, there is provided the pharmaceutical composition as described herein for use in treating a graft or transplant-related condition.

In one aspect, there is provided the pharmaceutical composition as described herein for use in treating a neurodegenerative disease.

In one aspect, there is provided the pharmaceutical composition as described herein for use in treating inflammation.

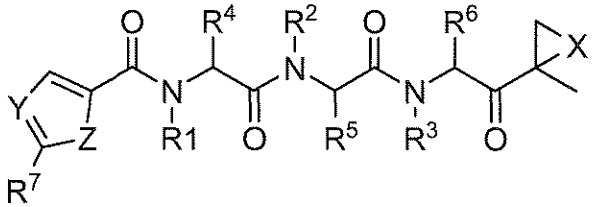
In one aspect, there is provided the pharmaceutical composition as described herein for use in treating a fibrotic-associated condition.

In one aspect, there is provided the pharmaceutical composition as described herein for use in treating an ischemic-related condition.

In one aspect, there is provided the pharmaceutical composition as described herein for use in treating an infection.

In one aspect, there is provided the pharmaceutical composition as described herein for use in treating a disease associated with bone loss.

One embodiment of the 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;

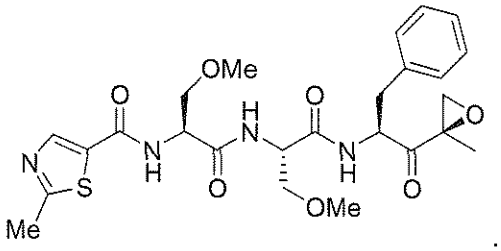
Y is N, , S, or $C(R^8)_2$, preferably NH;

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

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

Claims

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



(II)

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

3. The pharmaceutical composition of claim 2, wherein the orally administrable composition is selected from the group consisting of a tablet, a capsule, a granule, a powder and a syrup.

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

5. The pharmaceutical composition of claim 3, wherein the orally administrable composition is a capsule.

6. The pharmaceutical composition of claim 3, wherein the orally administrable composition is a granule.

7. The pharmaceutical composition of claim 3, wherein the orally administrable composition is a powder.

8. The pharmaceutical composition of claim 1, wherein the composition is a parenterally administrable composition.

9. The pharmaceutical composition of any one of claims 1 to 8, wherein the crystalline compound exhibits a differential scanning calorimetry (DSC) thermogram characterized with an endothermic peak at 147°C.

10. The pharmaceutical composition of any one of claims 1 to 9 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.

11. The pharmaceutical composition of any one of claims 1 to 10 for use in treating cancer.

12. The pharmaceutical composition for use of claim 11, 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.

13. The pharmaceutical composition of any one of claims 1 to 10 for use in treating 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.

14. The pharmaceutical composition of any one of claims 1 to 10 for use in treating multiple myeloma.

15. The pharmaceutical composition of any one of claims 1 to 10 for use in treating Waldenstrom's macroglobulinemia.

16. The pharmaceutical composition of any one of claims 1 to 10 for use in treating a cancer selected from hematological cancers, Waldenstrom's macroglobulinemia, multiple lyeloma, diffuse B cell lymphoma, mantle cell lymphoma, pancreatic cancer and lung cancer.

17. The pharmaceutical composition of any one of claims 1 to 10 for use in treating myodisplastic syndrome or myeloproliferative disease.

18. The pharmaceutical composition of any one of claims 1 to 10 for use in treating an autoimmune disease.

19. The pharmaceutical composition for use of claim 18, wherein the autoimmune disease is selected from the group consisting of lupus, rheumatoid arthritis, and antigen presentation.

20. The pharmaceutical composition of any one of claims 1 to 10 for use in treating a graft or transplant-related condition.

21. The pharmaceutical composition for use of claim 20, wherein the graft or transplant-related condition is graft-versus-host disease.

22. The pharmaceutical composition of any one of claims 1 to 10 for use in treating a neurodegenerative disease.

23. The pharmaceutical composition of any one of claims 1 to 10 for use in treating inflammation.

24. The pharmaceutical composition of any one of claims 1 to 10 for use in treating a fibrotic-associated condition.

25. The pharmaceutical composition of any one of claims 1 to 10 for use in treating an ischemic-related condition.

26. The pharmaceutical composition for use of claim 25, wherein the ischemic-related condition is heart failure.

27. The pharmaceutical composition of any one of claims 1 to 10 for use in treating an infection.

28. The pharmaceutical composition of any one of claims 1 to 10 for use in treating a disease associated with bone loss.

29. The pharmaceutical composition for use of claim 28, wherein the disease associated with bone loss is osteoporosis.