SOLID FORMS OF A TRIAZINE DERIVATIVE AS CBL-B MODULATOR

CROSS-REFERENCE TO RELATED APPLICATION

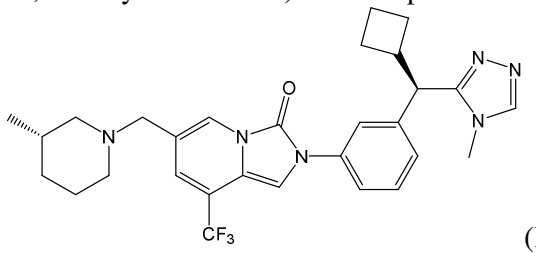
[001] This application claims the benefit of, and priority to, U.S. Patent Application No. 63/388,342, filed on July 12, 2022, the content of which is hereby incorporated by reference in its entirety.

BACKGROUND

[002] Cbl-b is a E3 ubiquitin-protein ligase that functions as a negative regulator of T-cell activation. Modulation of Cbl-b has been shown to be a therapeutic target for a variety of diseases and disorders. There remains an unmet need to develop solid forms (e.g., crystalline forms) of compounds that inhibit Cbl-b that are suitable for administration to patients with conditions, diseases, or disorders, such as cancer.

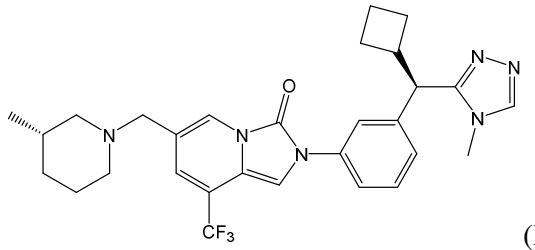
SUMMARY

[003] In one example, provided herein are crystalline forms (e.g., anhydrous crystalline forms, crystalline solvates, and crystalline salts) of a compound of formula (I)



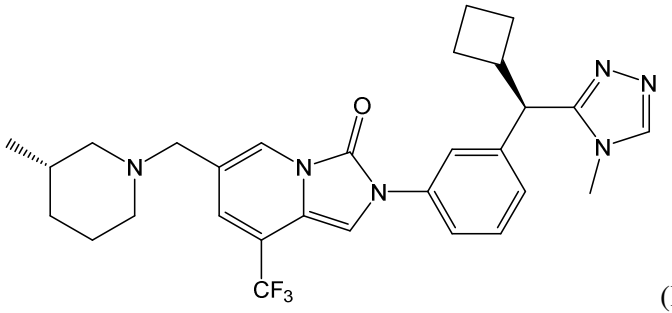
(I).

[003a] In one aspect, the present disclosure refers to a crystalline form of a compound of formula (I):



(I).

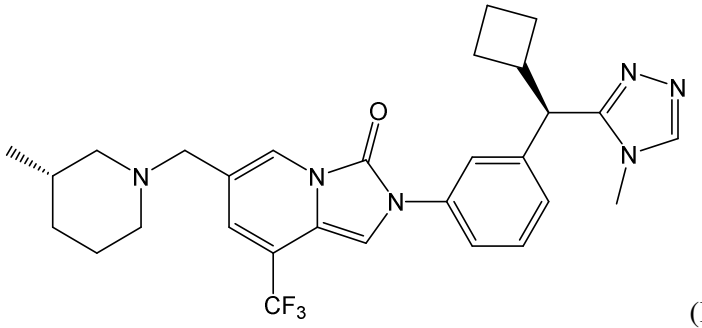
[004] In various examples, a crystalline form of a compound of formula (I):



(I),

wherein the crystalline form is characterized by an X-ray powder diffraction pattern comprising one or more peaks selected from 6.0° ± 0.2°, 8.6° ± 0.2°, 14.3° ± 0.2°, and 16.3° ± 0.2° 2-theta.

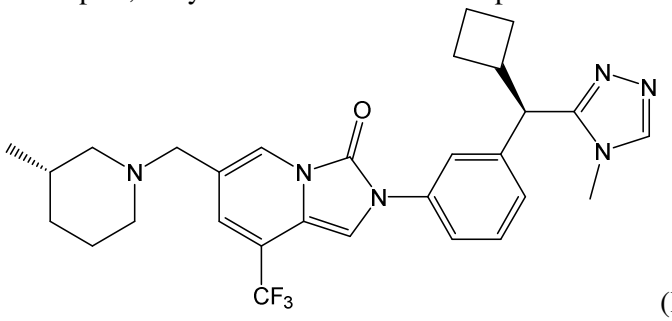
[004a] In one aspect, the present disclosure refers to a crystalline form of a compound of formula (I):



(I),

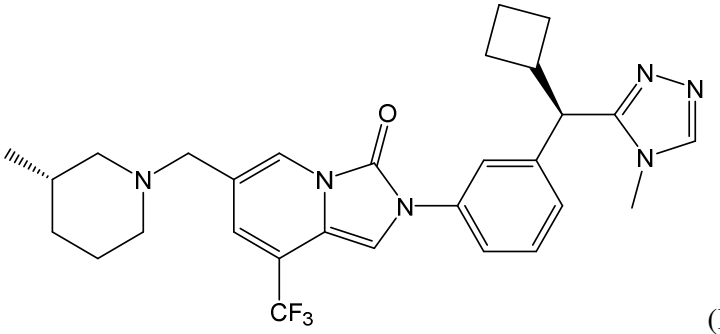
wherein the crystalline form is characterized by an X-ray powder diffraction (XRPD) pattern comprising one or more peaks selected from 6.0° ± 0.2°, 8.6° ± 0.2°, 14.3° ± 0.2°, and 16.3° ± 0.2° 2-theta.

[005] In various examples, a crystalline solvate of a compound of formula (I):



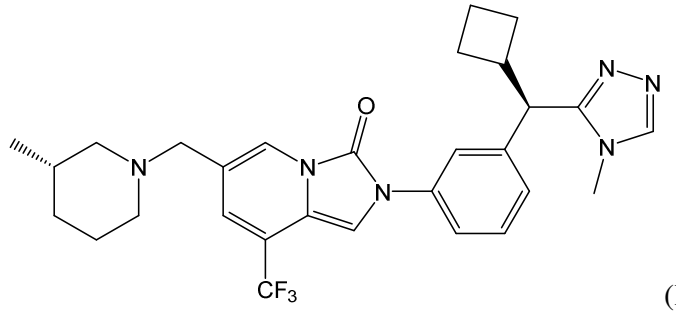
(I).

[005a] In one aspect, the present disclosure refers to a crystalline solvate of a compound of formula (I):



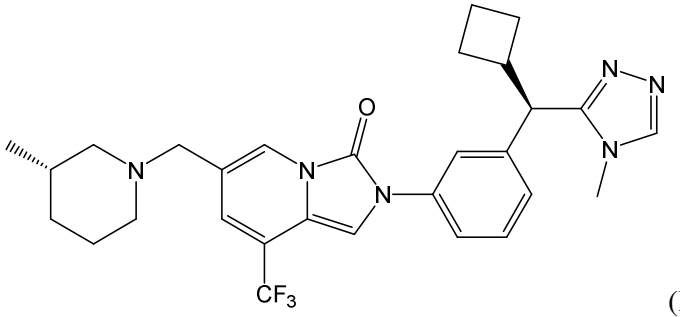
(I).

[006] In various examples, a crystalline acetone solvate of a compound of formula (I):



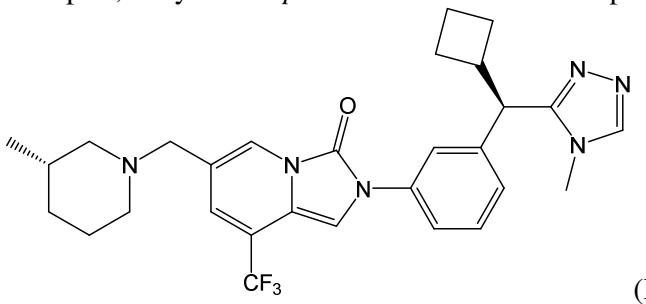
(I).

[006a] In one aspect, the present disclosure refers to a crystalline acetone solvate of a compound of formula (I):



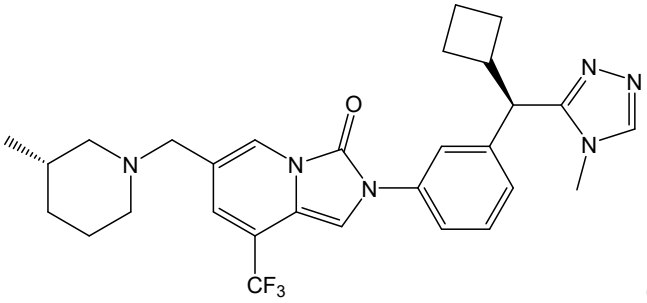
(I).

[007] In various examples, a crystalline *p*-dioxane solvate of a compound of formula (I):



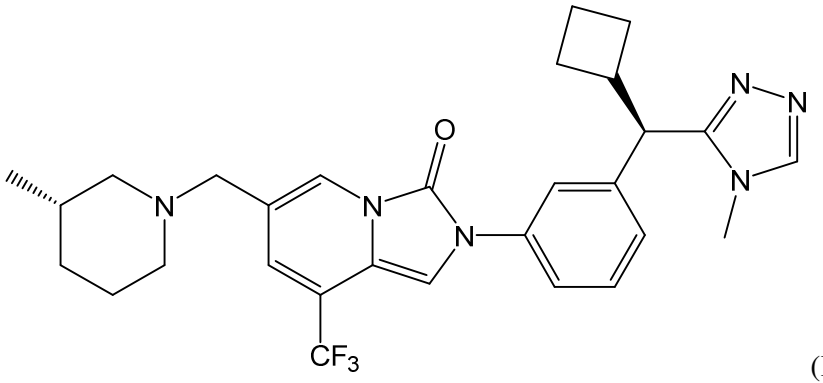
(I).

[007a] In one aspect, the present disclosure refers to a crystalline *p*-dioxane solvate of a compound of formula (I):



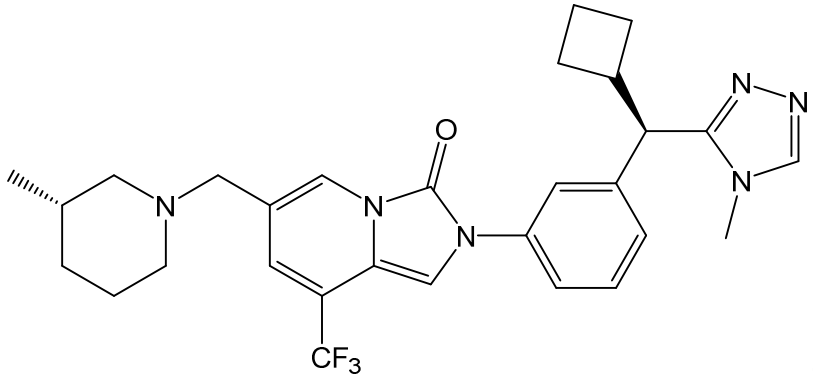
(I).

[008] In various examples, a crystalline tetrahydrofuran solvate of a compound of formula (I):



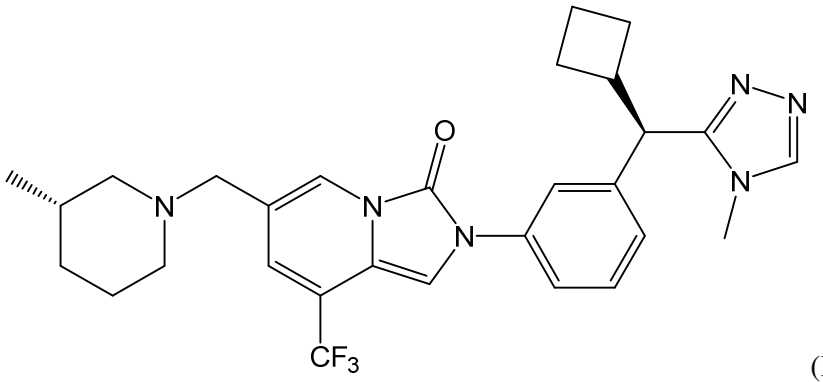
(I).

[008a] In one aspect, the present disclosure refers to a crystalline tetrahydrofuran solvate of a compound of formula (I):



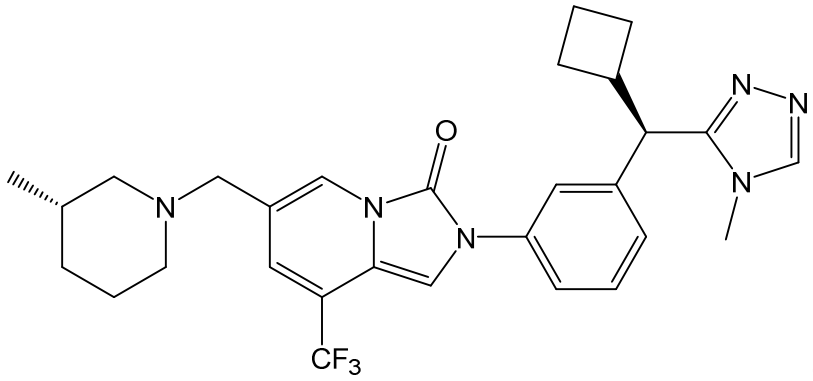
(I).

[009] In various examples, a crystalline citrate salt of a compound of formula (I):



(I).

[009a] In one aspect, the present disclosure refers to a crystalline citrate salt of a compound of formula (I):



(I).

[010] In another example, provided herein are pharmaceutical compositions comprising a crystalline form of the compound of formula (I) described herein and a pharmaceutically acceptable excipient.

[010a] In one aspect, the present disclosure refers to a pharmaceutical composition comprising: the crystalline form as disclosed herein, the crystalline solvate as disclosed herein, or the crystalline citrate salt as disclosed herein; and a pharmaceutically acceptable excipient.

[011] In another example, provided herein are crystalline forms of the compound of formula (I) (e.g., anhydrous crystalline forms, crystalline solvates, and crystalline salts) and pharmaceutical compositions which are useful for the treatment of the various conditions, diseases, and disorders described herein in a subject in need thereof. In certain examples, the condition, disease, or disorder is associated with cell proliferation. In certain examples, the condition, disease, or disorder associated with cell proliferation is hyperplasia or a cancer. In certain examples, the cancer is a hematologic cancer (e.g., lymphoma, leukemia, and myeloma). In certain examples, the cancer is a non-hematologic cancer (e.g., a carcinoma or a sarcoma). In certain examples, administration of a crystalline form of the compound of formula (I) or pharmaceutical composition described herein results in the subject exhibiting one or more of the following: increased T-cell activation, increased T-cell proliferation, decreased T-cell exhaustion, decreased T-cell anergy, and decreased T-cell tolerance. In certain examples, increased T-cell activation comprises increased production of a cytokines. In certain examples, administration of a

crystalline form of the compound of formula (I) or pharmaceutical composition described herein results in the subject exhibiting increased NK-cell activation. In certain examples, increased NK-cell activation comprises increased production of cytokines.

[011a] In one aspect, the present disclosure refers to a method of treating a disease or condition associated with cell proliferation comprising administering a therapeutically effective amount of a crystalline form as disclosed herein, a crystalline solvate as disclosed herein, a crystalline citrate salt as disclosed herein, or a pharmaceutical composition as disclosed herein to a subject in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[012] FIG. 1 is an exemplary X-ray powder diffraction (XRPD) pattern of the anhydrous crystalline form of the compound of formula (I), as further described in Example 2.

[013] FIG. 2 is an atomic displacement ellipsoid diagram for the anhydrous crystalline form of the compound of formula (I), as further described in Example 2.

[014] FIG. 3 is an exemplary proton nuclear magnetic resonance (^{1}H NMR) spectrum of the anhydrous crystalline form of the compound of formula (I) dissolved in dimethylsulfoxide-d_6 containing trimethylsilane, as further described in Example 2.

[015] FIG. 4 shows exemplary differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) thermograms for the anhydrous crystalline form of the compound of formula (I), as further described in Example 2.

[016] FIG. 5 is an exemplary water sorption isotherm of the anhydrous crystalline form of the compound of formula (I), as further described in Example 2.

[017] FIG. 6 is an exemplary XRPD pattern of the crystalline acetone solvate of the compound of formula (I), as further described in Example 3.

[018] FIG. 7 is an exemplary XRPD indexing solution for the crystalline acetone solvate of the compound of formula (I), as further described in Example 3.

[019] FIG. 8 is an exemplary ^{1}H NMR spectrum of the crystalline acetone solvate of the compound of formula (I) dissolved in dimethylsulfoxide-d_6 containing trimethylsilane, as further described in Example 3.

[020] FIG. 9 shows exemplary DSC and TGA thermograms for the crystalline acetone solvate of the compound of formula (I), as further described in Example 3.

[021] FIG. 10 is an exemplary XRPD pattern of the crystalline *p*-dioxane solvate of the compound of formula (I), as further described in Example 4.

[022] FIG. 11 is an exemplary XRPD indexing solution for the crystalline *p*-dioxane solvate of the compound of formula (I), as further described in Example 4.

[023] FIG. 12 is an exemplary ^{1}H NMR spectrum of the crystalline *p*-dioxane solvate of the compound of formula (I) dissolved in dimethylsulfoxide-d_6 containing trimethylsilane, as further described in Example 4.