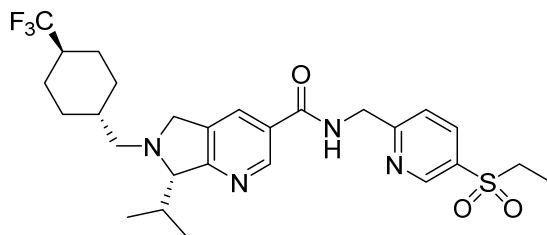


5472.CAN-10-2907, Epub 2011 Feb 8; Su *et al.*, 2014, Immunol. Res., 58:118-124, doi: 10.1007/s12026-013-8483-y, Epub 2014 Jan 9; Carmi *et al.*, 2011, J. Immunol., 186:3462-3471, doi: 10.4049/jimmunol.1002901, Epub 2011 Feb 7; Chen *et al.*, 2013, Histopathology, 63:225-233, doi: 10.1111/his.12156, Epub 2013 Jun 6).

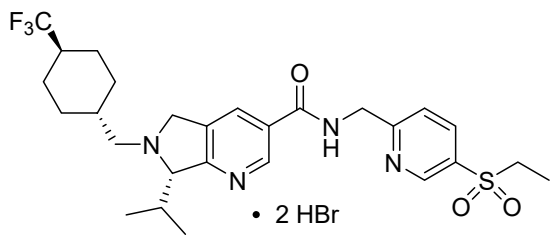
- 5 [0004] Compound **1** is an inhibitor of ROR γ and has therapeutic properties against a number of ROR γ mediated diseases. Compound **1** is exemplified in U.S. Patent No. 9,266,886 and has the formula:



- 10 [0005] Despite its potential for commercialization, Compound **1** is susceptible to oxidation, particularly in solution. This makes it difficult to formulate pharmaceutically acceptable salts and polymorphs which are amendable to large scale manufacturing and formulating. Thus, the need to generate alternative forms for this potent inhibitor remains.

SUMMARY

- 15 [0005a] In one aspect of the present disclosure, there is provided a crystalline Form D bis-hydrogen bromide salt having the formula:



- 20 wherein the crystalline Form D bis-hydrogen bromide salt is characterized by at least three x-ray powder diffraction peaks at 2θ angles selected from 14.24°, 15.24°, 15.90°, 18.54°, 18.82°, and 22.46°; and wherein the crystalline Form D bis-hydrogen bromide salt has a purity of >95%.

[0006] In one example, provided herein are stable hydrogen bromide salt forms of Compound **1**. Unlike other salt forms, the disclosed HBr salts can be prepared with minimal concern for degradation or minimal need for special precautions such as working in oxygen free atmospheres. See e.g., the Exemplification section below.

[0007] In another example, specific mono- and bis-hydrogen bromide crystalline salts of Compound **1** are disclosed, as well as methods for their preparation. Of the five characterized crystalline salt forms, Form D was found to have significantly less moisture uptake than other solid forms and to be more reproducible at large scale syntheses, thus making this form an attractive option for commercial processing.

[0008] During production of the bis-hydrogen bromide salt, initial attempts employed a two-step process started from Compound **1**. This process involved the formation and isolation of a mono-hydrogen bromide salt by treatment with hydrobromic acid followed by a second independent treatment step with hydrobromic acid to form a bis-hydrogen bromide salt of Compound **1**. This two-step method was utilized because initial attempts to produce a purified version of the bis-hydrogen bromide salt directly (i.e., without first isolating the mono-bromide salt) did not afford the desired level of purity required for large batch

processing. The disclosed two-step method required the use of HBr and MeOH during the final steps of the synthesis. This transformation led to contamination of the product from production of MeBr. This problem was subsequently solved by slurrying the product in a mixture of isopropyl acetate and water. Thus, in addition to the two step method and the formation of the mono- and bis-hydrogen bromide salt, disclosed herein are methods of removing methyl bromide from a composition comprising methyl bromide and crystalline form D bis-hydrogen bromide salt of Compound 1.

[0009] A one step process of forming the disclosed bis-hydrogen bromide salt directly from Compound 1 was also found. In this example, neutralizing the reductive amination reaction mixture, thereby resulting in precipitation, provided Compound 1 as a free base in high purity and good yield, particularly on a larger scale. For example, reactions were effective at >3 kg scale with 98% yield and in >99 area% purity. See e.g., the Exemplification section. From this, treatment with a sufficient amount of hydrobromic acid afforded the desired bis-hydrogen bromide salt without the need to use MeOH. While no detectable contamination from MeBr was observed, this process led to the formation of a mixture of crystalline forms: Form E, Form F, and Form G. This problem, however, was solved by slurrying the product in a mixture of isopropyl acetate and water to afford a single bis-hydrogen bromide crystal form of Compound 1, i.e., Form D. Thus, in addition to the one-step process, provided herein are methods of converting crystalline Forms E, F and G of a bis-hydrogen bromide salt of Compound 1 to Form D crystalline bis-hydrogen bromide salt of Compound 1.

[0010] Also provided herein are methods of using the disclosed forms such treat a disease or disorder mediated by ROR γ .

BRIEF DESCRIPTION OF THE FIGURES

[0011] **FIG 1.** depicts an X-ray powder diffraction pattern (XRPD) for Form A of Compound 1.

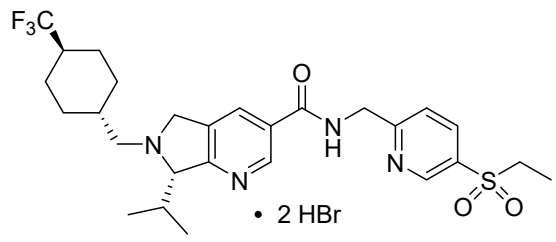
[0012] **FIG 2.** depicts a Differential Scanning Calorimetry (DSC) spectrum for Form A of Compound 1.

[0013] **FIG 3.** depicts a thermal gravimetric analysis (TGA) pattern for Form A of Compound 1.

[0014] **FIG 4.** depicts a Dynamic Vapor Sorption (DVS) isotherm plot for Form A of Compound 1.

WHAT IS CLAIMED IS:

1. A crystalline Form D bis-hydrogen bromide salt having the formula:



wherein the crystalline Form D bis-hydrogen bromide salt is characterized by at least three x-ray powder diffraction peaks at 2θ angles selected from 14.24° , 15.24° , 15.90° , 18.54° , 18.82° , and 22.46° ; and wherein the crystalline Form D bis-hydrogen bromide salt has a purity of $>95\%$.

2. The crystalline Form D bis-hydrogen bromide salt of Claim 1, wherein the crystalline form is characterized by at least four x-ray powder diffraction peaks at 2θ angles selected from 14.24° , 15.24° , 15.90° , 18.54° , 18.82° , and 22.46° .

3. The crystalline Form D bis-hydrogen bromide salt of Claim 1, wherein the crystalline form is characterized by at least five x-ray powder diffraction peaks at 2θ angles selected from 14.24° , 15.24° , 15.90° , 18.54° , 18.82° , and 22.46° .

4. The crystalline Form D bis-hydrogen bromide salt of Claim 1, wherein the crystalline form is characterized by x-ray powder diffraction peaks at 2θ angles at 14.24° , 15.24° , 15.90° , 18.54° , 18.82° , and 22.46° .

5. The crystalline Form D bis-hydrogen bromide salt of Claim 1, wherein the crystalline form is a solvate.

6. The crystalline Form D bis-hydrogen bromide salt of Claim 1, wherein the crystalline form is a hydrate.