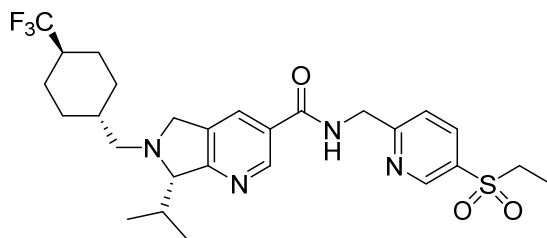


5472.CAN-10-2907, Epub 2011 Feb 8; Su *et al.*, 2014, Immunol. Res., 58:118-124, doi: 10.1007/s12026-013-8483-y, Epub 2014 Jan 9; Carmi *et al.*, 2011, J. Immunol., 186:3462-3471, doi: 10.4049/jimmunol.1002901, Epub 2011 Feb 7; Chen *et al.*, 2013, Histopathology, 63:225-233, doi: 10.1111/his.12156,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

[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:

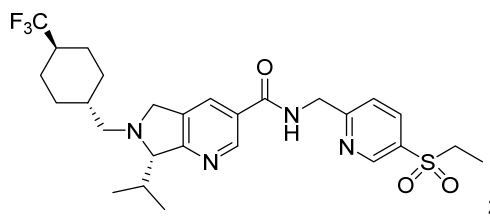


[0005] Despite its potential for commercialization, Compound **1** is susceptible to oxidation, particularly in solution. This makes it difficult to formulate pharmaceutically acceptable salts and polymorphs which are amenable to large scale manufacturing and formulating. Thus, the need to find alternative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

SUMMARY

[0006] A two-step method for the preparation of a bis-hydrogen bromide salt form of Compound **1** was identified. This process involved the formation and isolation of a mono-hydrogen bromide salt of Compound **1** 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 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 has been solved herein by slurrying the product in a mixture of isopropyl acetate and water. Thus, 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**.

[0006a] In one aspect of the present disclosure, there is provided a method of removing methyl bromide from a composition comprising methyl bromide and crystalline form D bis-hydrogen bromide salt of a compound having the following structural:



comprising:

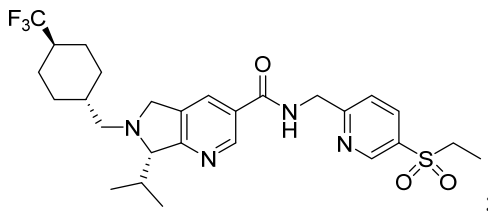
i) slurring the composition in a mixture of isopropyl acetate/water or a mixture of heptane/water; and

ii) separating the crystalline form D bis-hydrogen bromide salt from the mixture of isopropyl acetate/water or the mixture of heptane/water, wherein the bis-hydrogen bromide salt is of crystalline Form D 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° .

[0007] Also provided is a one step process for forming a bis-hydrogen bromide salt form of Compound 1. 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

Listing of Claims:

1. A method of removing methyl bromide from a composition comprising methyl bromide and crystalline form D bis-hydrogen bromide salt of a compound having the following structural:



comprising:

i) slurrying the composition in a mixture of isopropyl acetate/water or a mixture of heptane/water; and

ii) separating the crystalline form D bis-hydrogen bromide salt from the mixture of isopropyl acetate/water or the mixture of heptane/water, wherein the bis-hydrogen bromide salt is of crystalline Form D 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° .

2. The method of Claim 1, wherein the composition is slurried in a mixture of isopropyl acetate/water.

3. The method of Claim 1 or 2, wherein the composition is slurried in a mixture of isopropyl acetate comprising 0.25% to 2.5% v/v of water.

4. The method of any one of Claims 1 to 3, wherein the composition is slurried in a mixture of isopropyl acetate comprising 0.5% to 2.0 % v/v of water.

5. The method of any one of Claims 1 to 4, wherein the composition is slurried in a mixture of isopropyl acetate comprising 0.9% to 1.1 % v/v of water.

6. The method of any one of Claims 1 to 5, wherein the composition comprises greater than 45 ppm of methyl bromide prior to slurrying.

7. The method of any one of Claims 1 to 6, wherein the crystalline form D bis-hydrogen bromide salt after separation comprises less than 40 ppm of methyl bromide.
8. The method of any one of Claims 1 to 7, wherein the crystalline form D bis-hydrogen bromide salt after separation comprises an amount of methyl bromide that is below the level of detection.
9. The method of any one of Claims 1 to 8, wherein the crystalline form D bis-hydrogen bromide salt is separated by filtration.