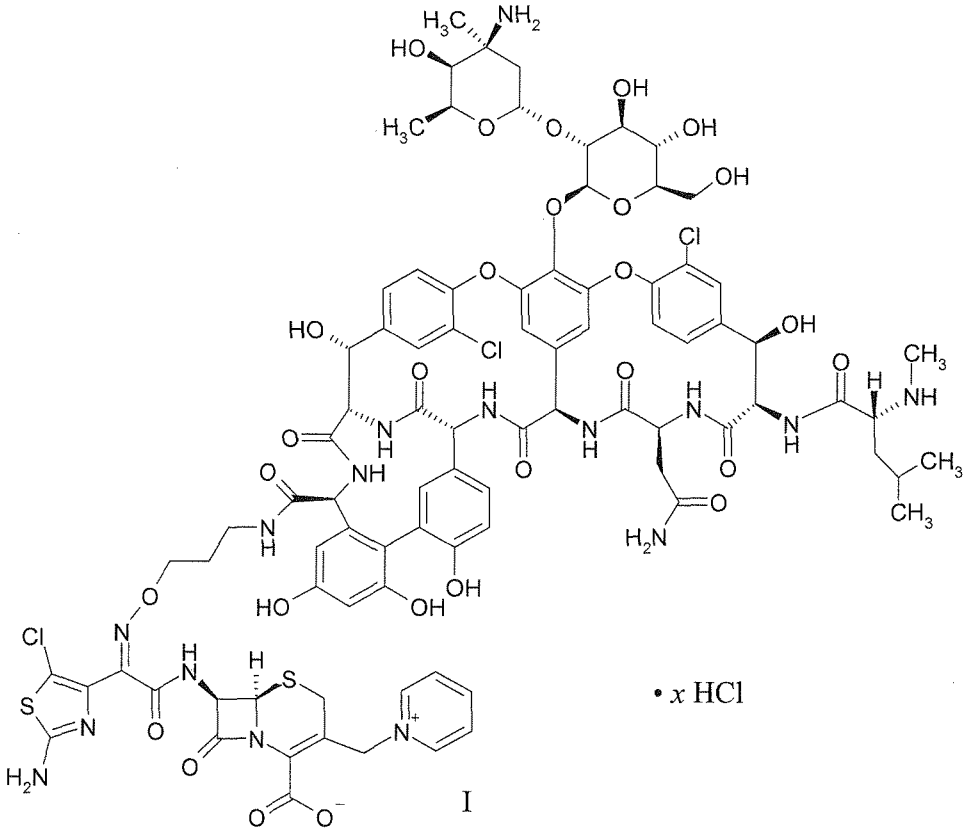
contradictory as to which excipient to use with a particular pharmaceutical agent. As a result, identifying an excipient or combinations of excipients that improves the storage stability of a cross-linked cephalosporin-glycopeptide is particularly challenging since such compounds contain both cephalosporin and glycopeptide moieties in the same molecule.

SUMMARY

In an aspect, the present disclosure provides a compound of formula I:



• *x* HCl

I

wherein *x* is in the range of from ~~about~~ 1 to ~~about~~ 2.

Such hydrochloride salts have been discovered to have significantly improved storage stability at room temperature and at refrigerated temperature compared to the corresponding trihydrochloride salt. Additionally, the storage stability of such hydrochloride salts has been found to be further improved in compositions containing sucrose and glycine.

In one embodiment, *x* is about 1, i.e., the compound of formula I is a monohydrochloride salt. In another embodiment, *x* is about 2, i.e., the compound of formula I is a dihydrochloride salt.

In another embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of formula I. In one embodiment, the pharmaceutical composition comprises a pharmaceutically acceptable carrier and a compound of formula I. In a particular embodiment, the pharmaceutical composition contains sucrose and glycine. In an aspect, the present disclosure provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula I as disclosed herein. In another aspect, the present disclosure provides a pharmaceutical composition comprising (a) a compound of formula I as disclosed herein; (b) sucrose and (c) glycine or a pharmaceutically-acceptable salt thereof.

In yet another aspect, the present disclosure provides a pharmaceutical composition comprising:

(a) a compound of formula I as disclosed herein;

(b) ~~about~~ 0.5 to ~~about~~ 2.0 parts by weight of sucrose; and

(c) ~~about~~ 0.5 to ~~about~~ 2.0 parts by weight of glycine (as the free base equivalent);

wherein the parts by weight of sucrose and glycine are based on the part by weight of the compound of formula I as disclosed herein (as the free base equivalent).

In a particular embodiment, the pharmaceutical composition is a lyophilized composition. In another particular embodiment, the pharmaceutical composition comprises about 1.0 part by weight of sucrose; and about 1.5 parts by weight of glycine. In yet another particular embodiment, the change in purity of the compound of formula I in the pharmaceutical composition is less than about 10 % as measured by high performance liquid chromatography after storage for 12 months at a temperature in the range of from about 18 °C to about 25 °C.

In another embodiment, the present disclosure provides a method for treating a bacterial infection in a patient using a compound of formula I. In one embodiment, the method comprises administering to the patient a compound of formula I. In another embodiment, the method comprises administering to the patient a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a compound of formula I.

In another aspect, the present disclosure provides a process for preparing a compound of formula I as disclosed herein. The process comprises the steps of:

(a) forming an aqueous composition comprising 26-[[[3-[[(*Z*)-[1-(2-amino-5-chloro-4-thiazolyl)-2-[[(6*R*,7*R*)-2-carboxy-8-oxo-3-(pyridiniomethyl)-5-thia-1-azabicyclo[4.2.0]oct-2-en-7-yl]amino]-2-oxoethylidene]amino]oxy]propyl]amino]-carbonyl]-26-decarboxyvancomycin and hydrochloric acid in a molar ratio of ~~about~~ 1:1 to ~~about~~ 1:2;

(b) lyophilizing the aqueous composition to provide a compound of formula I as disclosed herein.

In another embodiment, the present disclosure provides a product produced by a process described herein.

In another aspect, the present disclosure provides a method for reducing the degradation of 26-[[[3-[[(*Z*)-[1-(2-amino-5-chloro-4-thiazolyl)-2-[[(6*R*,7*R*)-2-carboxy-8-oxo-3-(pyridiniomethyl)-5-thia-1-azabicyclo[4.2.0]oct-2-en-7-yl]amino]-2-oxoethylidene]-amino]oxy]propyl]amino]-carbonyl]-26-decarboxyvancomycin during storage. The method comprises (a) forming a compound of formula I as disclosed herein and (b) storing the compound of formula I as disclosed herein at a temperature in the range of from ~~about~~ -25 °C to ~~about~~ 25 °C. In another embodiment, the compound of formula I is stored at about 2 °C to about 8 °C.

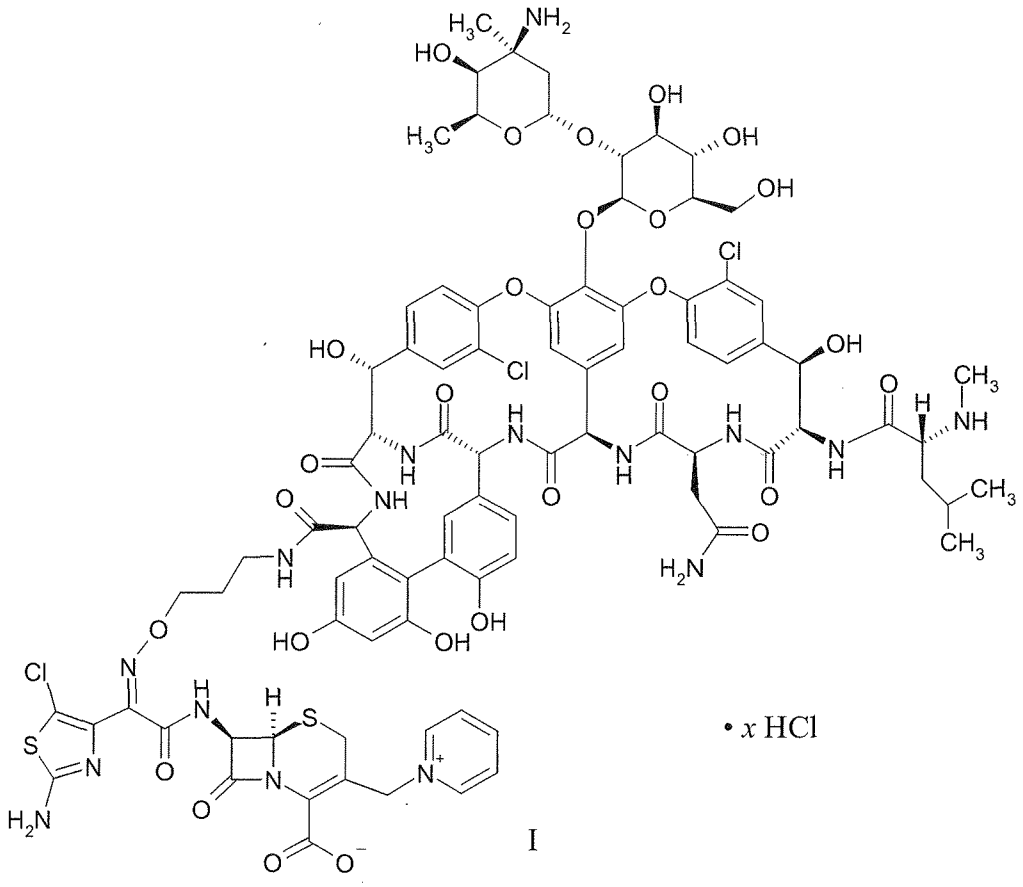
In another aspect, the present disclosure provides a method for reducing the degradation of 26-[[[3-[[(*Z*)-[1-(2-amino-5-chloro-4-thiazolyl)-2-[[(6*R*,7*R*)-2-carboxy-8-oxo-3-(pyridiniomethyl)-5-thia-1-azabicyclo[4.2.0]oct-2-en-7-yl]amino]-2-oxoethylidene]-amino]oxy]propyl]amino]-carbonyl]-26-decarboxyvancomycin during storage. The method comprises (a) forming a pharmaceutical composition as disclosed above and (b) storing the pharmaceutical composition at a temperature in the range of from ~~about~~ -25 °C to ~~about~~ 25 °C.

In yet another embodiment, the method comprises storing a pharmaceutical composition comprising (a) a compound of formula I; (b) about 0.5 to about 2.0 parts by weight of sucrose; and (c) about 0.5 to about 2.0 parts by weight of glycine (as the free base equivalent); wherein the parts by weight of sucrose and glycine are per part by weight of the compound of formula I (as the free base equivalent), at a temperature in the range of from about -25 °C to about 25 °C. In another embodiment, the pharmaceutical composition is stored at about 2 °C to about 8 °C.

Other embodiments of this disclosure are disclosed herein.

WHAT IS CLAIMED IS:

1. A compound of formula I:



• *x* HCl

I

wherein *x* is in the range of from ~~about~~ 1 to ~~about~~ 2.

2. The compound of Claim 1, wherein *x* is ~~about~~ 1.

3. The compound of Claim 1, wherein *x* is ~~about~~ 2.

4. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Claim 1, 2 or 3.

5. A pharmaceutical composition comprising (a) a compound of Claim 1, 2 or 3; (b) sucrose and (c) glycine or a pharmaceutically-acceptable salt thereof.

6. The pharmaceutical composition of Claim 5, wherein the composition is a lyophilized composition.

7. A pharmaceutical composition comprising:

(a) a compound of Claim 1, 2 or 3;

(b) ~~about~~ 0.5 to ~~about~~ 2.0 parts by weight of sucrose; and

(c) ~~about~~ 0.5 to ~~about~~ 2.0 parts by weight of glycine (as the free base equivalent);

wherein the parts by weight of sucrose and glycine are based on the part by weight of the compound of Claim 1, 2 or 3 (as the free base equivalent) .

8. The pharmaceutical composition of Claim 6, wherein the composition comprises ~~about~~ 1.0 part by weight of sucrose; and ~~about~~ 1.5 parts by weight of glycine.

9. The pharmaceutical composition of Claim 8, wherein change in purity of the compound of Claim 1, 2 or 3 (as the free base equivalent) in the pharmaceutical composition is less than ~~about~~ 10 % as measured by high performance liquid chromatography after storage for 12 months at a temperature in the range of from ~~about~~ 18 °C to ~~about~~ 25 °C.

10. Use of the compound of Claim 1, 2 or 3 in the manufacture of a medicament for treating a bacterial infection in a patient.

11. Use of a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a compound of Claim 1, 2, or 3 in the manufacture of a medicament for treating a bacterial infection in a patient.

12. A compound of Claim 1, 2 or 3 for use in therapy.

13. A process for preparing a compound of Claim 1, the process comprising the steps of:

(a) forming an aqueous composition comprising 26-[[[3-[[(*Z*)-[1-(2-amino-5-chloro-4-thiazolyl)-2-[[(6*R*,7*R*)-2-carboxy-8-oxo-3-(pyridiniomethyl)-5-thia-1-azabicyclo[4.2.0]oct-2-en-7-yl]amino]-2-oxoethylidene]amino]oxy]propyl]amino]-carbonyl]-26-decarboxyvancomycin and hydrochloric acid in a molar ratio of ~~about~~ 1:1 to ~~about~~ 1:2;

(b) lyophilizing the aqueous composition to provide a compound of Claim 1.

14. The process of Claim 13, wherein the molar ratio is ~~about~~ 1:1.

15. The process of Claim 13, wherein the molar ratio is ~~about~~ 1:2.

16. A method for reducing the degradation of 26-[[[3-[[(*Z*)-[1-(2-amino-5-chloro-4-thiazolyl)-2-[[(6*R*,7*R*)-2-carboxy-8-oxo-3-(pyridiniomethyl)-5-thia-1-azabicyclo[4.2.0]oct-2-en-7-yl]amino]-2-oxoethylidene]-amino]oxy]propyl]amino]-carbonyl]-26-decarboxyvancomycin during storage, the method comprising (a) forming a compound of Claim 1, 2 or 3 and (b) storing the compound of Claim 1, 2 or 3 at a temperature in the range of from ~~about~~ -25 °C to ~~about~~ 25 °C.

17. The method of Claim 16, wherein the temperature is in the range of from ~~about~~ 2 °C to ~~about~~ 8 °C.

18. A method for reducing the degradation of 26-[[[3-[[(*Z*)-[1-(2-amino-5-chloro-4-thiazolyl)-2-[[(6*R*,7*R*)-2-carboxy-8-oxo-3-(pyridiniomethyl)-5-thia-1-azabicyclo[4.2.0]oct-2-en-7-yl]amino]-2-oxoethylidene]-amino]oxy]propyl]amino]-carbonyl]-26-decarboxyvancomycin during storage, the method comprising (a) forming a pharmaceutical composition of Claim 8 and (b) storing the pharmaceutical composition at a temperature in the range of from ~~about~~ -25 °C to ~~about~~ 25 °C.

19. The method of Claim 18, wherein the temperature is in the range of from ~~about~~ 2 °C to ~~about~~ 8 °C.