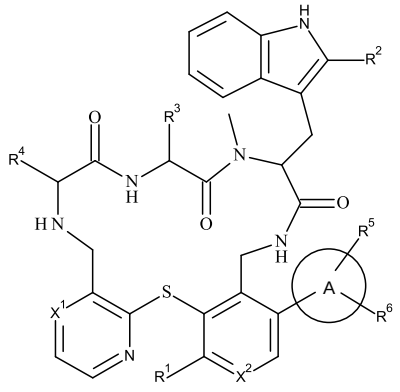
Acinetobacter baumannii has been defined and still remains "a prime example of a mismatch between unmet medical needs and the current antimicrobial research and development pipeline" according to the Antimicrobial Availability Task Force (AATF) of the Infectious Diseases Society of America (IDSA). Thus, there is a high demand and need to identify compounds suitable for the treatment of diseases and infections caused by *Acinetobacter baumannii*.

WO2017/072062 discloses peptide macrocycles that are active against *Acinetobacter baumannii*. However, there is still a high unmet need for improved compounds suitable for the treatment of diseases and infections caused by *Acinetobacter baumannii*.

Summary

The present disclosure provides a compound of formula (I)



(I)

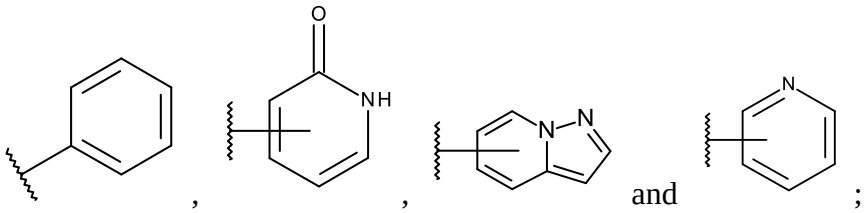
or a pharmaceutically acceptable salt thereof,

wherein:

X^1 is CH or N;

X^2 is CH or N;

A is selected from:



;

R^1 is selected from hydrogen, halogen, C_{1-6}-alkoxy and C_{1-6}-alkyl;

R^2 is hydrogen or C_{1-6}-alkyl;

R^3 is C_{1-6}-aminoalkyl;

R^4 is C_{1-6}-aminoalkyl or carbamoyl-C_{1-6}-alkyl;

R^5 is selected from carboxy, carboxy-C_{1-6}-alkyl and carboxy-C_{2-6}-alkenyl; and

R^6 is selected from hydrogen, halogen, hydroxy, C_{1-6}-alkoxy and C_{1-6}-alkylsulfonyl;

provided that said compound of formula (I) is not:

4-[(11S,14S,17S)-14-(4-Amino-butyl)-11-(3-amino-propyl)-25-chloro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentaaza-tricyclo[19.4.0.0*3,8*]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]-benzoic acid.

In one aspect, the present disclosure provides a compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]benzoic acid;

2-chloro-4-[rac-(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-25-chloro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,7,10,13,16,19-hexazatricyclo[19.4.0.03,8]pentacosa-1(21),3,5,7,22,24-hexaen-22-yl]benzoic acid;

4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-25-fluoro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]benzoic acid;

4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-25-chloro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]-2-methylsulfonyl-benzoic acid;

4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-16-methyl-17-[(2-methyl-1H-indol-3-yl)methyl]-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3,5,7,21,23-hexaen-22-yl]benzoic acid;

4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-17-(1H-indol-3-ylmethyl)-16,25-dimethyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]benzoic acid;

2-methoxy-4-[rac-(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-25-chloro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,7,10,13,16,19-hexazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]benzoic acid;

2-[4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-25-fluoro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]-2-oxo-1-pyridyl]acetic acid;

4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-17-(1H-indol-3-ylmethyl)-25-methoxy-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]benzoic acid;

5-[(11S,14S,17S)-11,14-bis(3-aminopropyl)-25-fluoro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]pyridine-2-carboxylic acid;

2-[4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-25-chloro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(21),3,5,7,22,24-hexaen-22-yl]-2-oxo-1-pyridyl]acetic acid;

2-[4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-17-(1H-indol-3-ylmethyl)-16,25-dimethyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]-2-oxo-1-pyridyl]acetic acid;

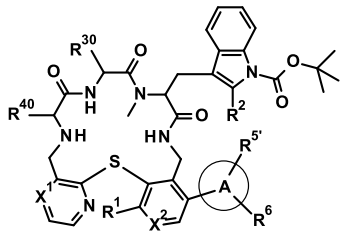
4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19,24-hexazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]benzoic acid;

2-[4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-25-chloro-16-methyl-17-[(2-methyl-1H-indol-3-yl)methyl]-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]-2-oxo-1-pyridyl]acetic acid; and

5-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-25-chloro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]pyrazolo[1,5-a]pyridine-2-carboxylic acid.

The present disclosure provides a process for the manufacture of the compounds of formula (I) described herein, comprising:

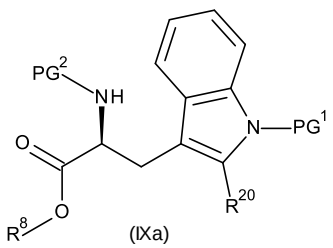
a) cleaving all amino-, indole- and carboxy protecting groups present in a compound of formula (VI), wherein R^1, R^2, $R^{5'}$, R^6, R^{30}, R^{40}, X^1 and $X^2$are as defined herein,



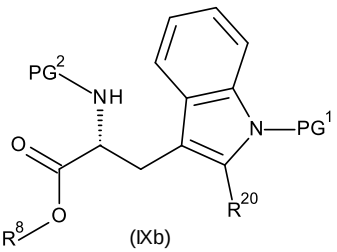
(VI)

to afford said compound of formula (I).

The present disclosure provides a process for the manufacture of compounds of formula (IXa) or (IXb), wherein PG^1 is a suitable protecting group for the indole nitrogen, PG^2 is a suitable amino protecting group and R^8 and R^{20} are each independently C_{1-6}-alkyl,



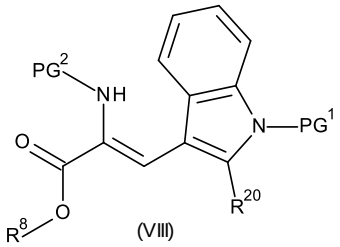
(IXa)



(IXb)

comprising:

asymmetric hydrogenation of a compound of formula (VIII), wherein PG^1 is a suitable protecting group for the indole nitrogen, PG^2 is a suitable amino protecting group and R^8 and R^{20} are each independently C_{1-6}-alkyl, in the presence of a homogeneous catalyst



(VIII)

to afford said compound of formula (IXa) or (IXb).

The present disclosure provides a compound of formula (I) described herein, obtainable by a process described herein.

The present disclosure provides a pharmaceutical composition comprising a compound of formula (I) described herein or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.

In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

The present disclosure provides a compound of formula (I) described herein or a pharmaceutically acceptable salt thereof or a pharmaceutical composition described herein for use as therapeutically active substance.

The present disclosure provides a compound of formula (I) described herein or a pharmaceutically acceptable salt thereof or a pharmaceutical composition described herein for use as an antibiotic.

The present disclosure provides a compound of formula (I) described herein or a pharmaceutically acceptable salt thereof or a pharmaceutical composition described herein for use in the treatment or prevention of infections and resulting diseases caused by *Acinetobacter baumannii*.

The present disclosure provides a method for the treatment or prevention of infections and resulting diseases caused by *Acinetobacter baumannii*, which method comprises administering a compound of formula (I) described herein or a pharmaceutically acceptable salt thereof or a pharmaceutical composition described herein to a human being or an animal.

The present disclosure provides the use of a compound of formula (I) described herein or a pharmaceutically acceptable salt thereof or a pharmaceutical composition

described herein for the treatment or prevention of infections and resulting diseases caused by *Acinetobacter baumannii*.

The present disclosure provides the use of a compound of formula (I) described herein or a pharmaceutically acceptable salt thereof or a pharmaceutical composition described herein for the manufacture of a medicament for the treatment or prevention of infections and resulting diseases caused by *Acinetobacter baumannii*.

Detailed description of the invention

Definitions

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below.

Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein, unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. The invention is not restricted to the details of any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

The nomenclature used in this Application is based on IUPAC systematic nomenclature, unless indicated otherwise.

Claims

1. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]benzoic acid;

2-chloro-4-[rac-(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-25-chloro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,7,10,13,16,19-hexazatricyclo[19.4.0.03,8]pentacosa-1(21),3,5,7,22,24-hexaen-22-yl]benzoic acid;

4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-25-fluoro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]benzoic acid;

4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-25-chloro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]-2-methylsulfonyl-benzoic acid;

4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-16-methyl-17-[(2-methyl-1H-indol-3-yl)methyl]-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3,5,7,21,23-hexaen-22-yl]benzoic acid;

4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-17-(1H-indol-3-ylmethyl)-16,25-dimethyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]benzoic acid;

2-methoxy-4-[rac-(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-25-chloro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,7,10,13,16,19-hexazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]benzoic acid;

2-[4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-25-fluoro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]-2-oxo-1-pyridyl]acetic acid;

4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-17-(1H-indol-3-ylmethyl)-25-methoxy-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]benzoic acid;

5-[(11S,14S,17S)-11,14-bis(3-aminopropyl)-25-fluoro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]pyridine-2-carboxylic acid;

2-[4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-25-chloro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(21),3,5,7,22,24-hexaen-22-yl]-2-oxo-1-pyridyl]acetic acid;

2-[4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-17-(1H-indol-3-ylmethyl)-16,25-dimethyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]-2-oxo-1-pyridyl]acetic acid;

4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19,24-hexazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]benzoic acid;

2-[4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-25-chloro-16-methyl-17-[(2-methyl-1H-indol-3-yl)methyl]-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]-2-oxo-1-pyridyl]acetic acid; and

5-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-25-chloro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]pyrazolo[1,5-a]pyridine-2-carboxylic acid.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

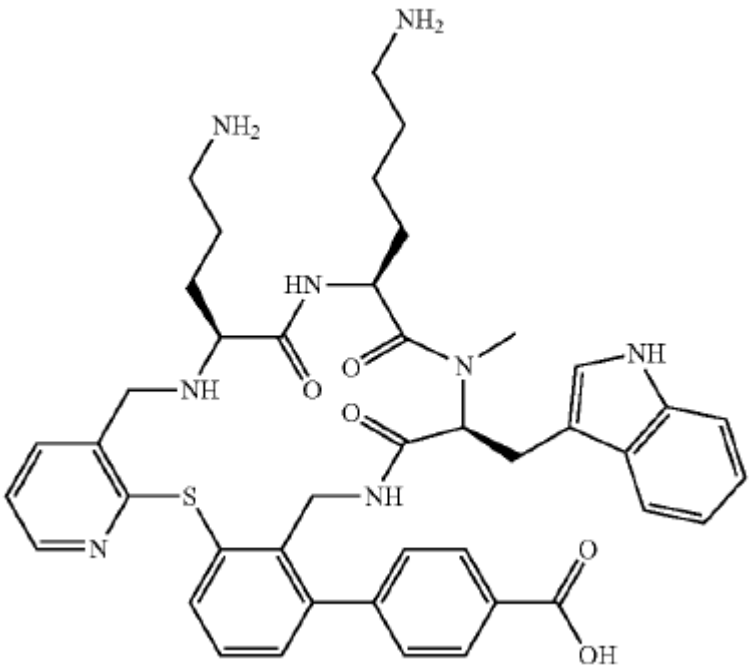
4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]benzoic acid;

2-[4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-25-chloro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(21),3,5,7,22,24-hexaen-22-yl]-2-oxo-1-pyridyl]acetic acid; and

4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19,24-hexazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]benzoic acid.

3. A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

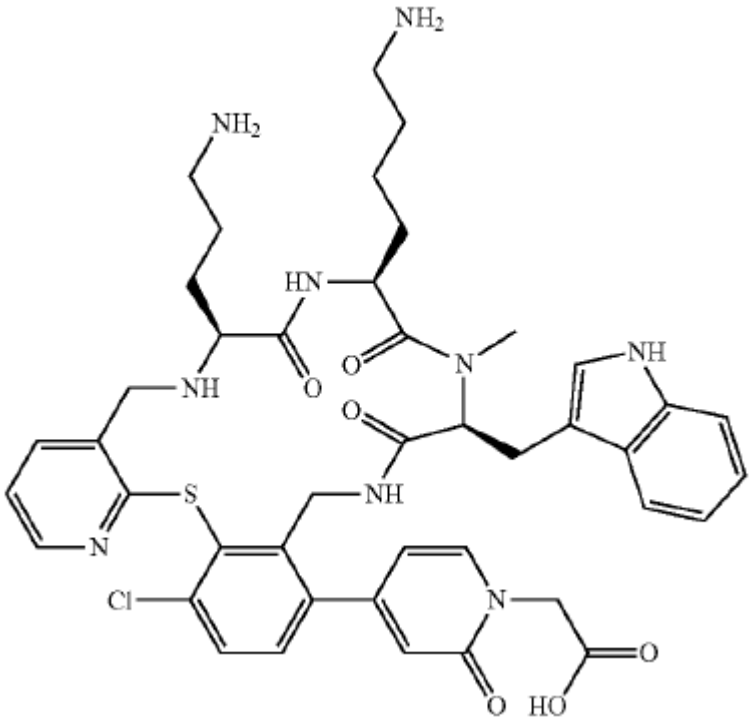
4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is



,

4-[(11S, 14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]benzoic acid.

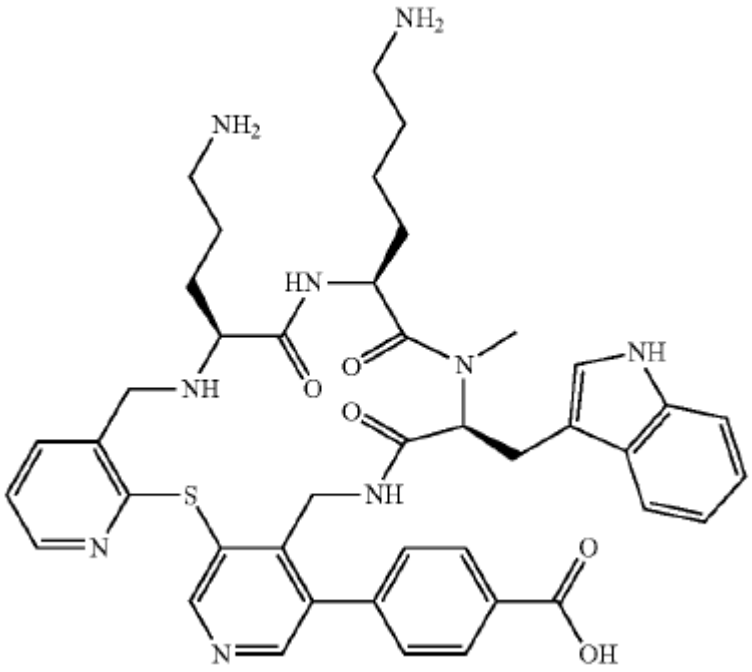
5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is



,

2-[4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-25-chloro-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19-pentazatricyclo[19.4.0.03,8]pentacosa-1(21),3,5,7,22,24-hexaen-22-yl]2-oxo-1-pyridyl]acetic acid.

6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is



,

4-[(11S,14S,17S)-14-(4-aminobutyl)-11-(3-aminopropyl)-17-(1H-indol-3-ylmethyl)-16-methyl-12,15,18-trioxo-2-thia-4,10,13,16,19,24-hexazatricyclo[19.4.0.03,8]pentacosa-1(25),3(8),4,6,21,23-hexaen-22-yl]benzoic acid.