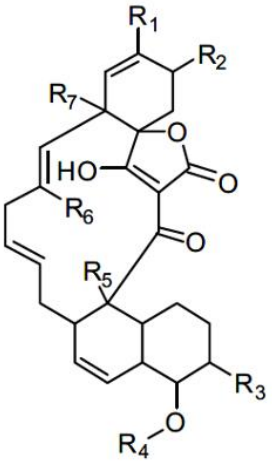
Summary

There is provided a compound of Formula (I) or a pharmaceutically acceptable salt, metabolite, prodrug or stereoisomer thereof:



Formula (I)

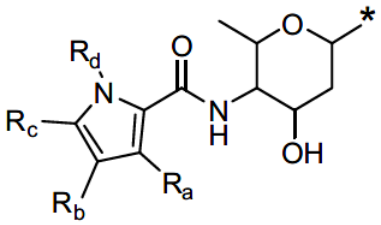
wherein:

R_2, R_3, R_5, R_6 and R_7 are independently selected from the group consisting of H, optionally substituted alkyl, optionally substituted alkenyl, and optionally substituted alkynyl;

R_1 is -COOH when R_6 is H;

R_1 is optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl when R_6 is optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl;

R_4 is H or of Formula (i):



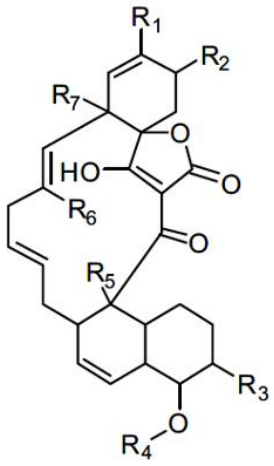
Formula (i)

wherein * represents the point of attachment to Formula (I);

R_d is H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl;

R_a, R_b, R_c are halogen.

In one aspect of the present disclosure, there is provided a compound of Formula (I) or a pharmaceutically acceptable salt, or stereoisomer thereof:



Formula (I)

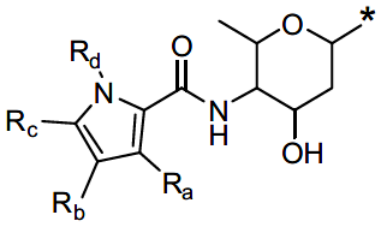
wherein:

R_2, R_3, R_5, R_6 and R_7 are independently selected from the group consisting of H, optionally substituted alkyl, optionally substituted alkenyl, and optionally substituted alkynyl;

R_1 is -COOH when R_6 is H;

R_1 is optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl when R_6 is optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl;

R_4 is H or of Formula (i):



Formula (i)

wherein * represents the point of attachment to Formula (I);

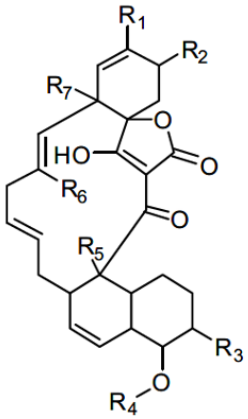
R_d is H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl;

R_a, R_b, R_c are halogen.

There is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, metabolite, prodrug or stereoisomer thereof, and a pharmaceutically acceptable excipient.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

There is provided a method of treating a bacterial, microbial and/or fungal infection, comprising administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, metabolite, prodrug or stereoisomer thereof, to a subject in need of treatment



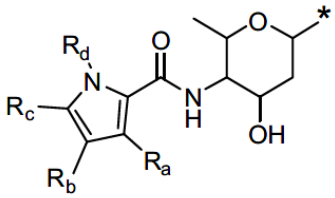
Formula (I)

wherein:

R_1 is -COOH, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl;

R_2, R_3, R_5, R_6 and R_7 are independently selected from the group consisting of H, optionally substituted alkyl, optionally substituted alkenyl, and optionally substituted alkynyl;

R_4 is H; or R_4 is of Formula (i):



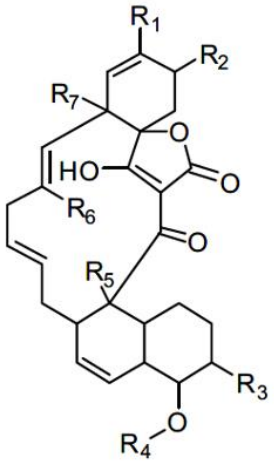
Formula (i)

wherein * represents the point of attachment to Formula (I); and

R_a, R_b, and R_c are independently selected from the group consisting of H, halogen, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl; and

R_d is H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl.

There is provided a method of treating cancer, comprising administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, metabolite, prodrug or stereoisomer thereof, to a subject in need of treatment



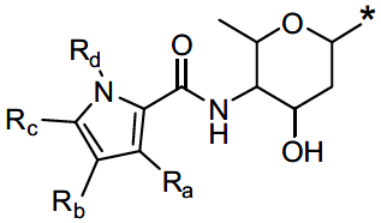
Formula (I)

wherein:

R_1 is -COOH, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl;

R_2, R_3, R_5, R_6 and R_7 are independently selected from the group consisting of H, optionally substituted alkyl, optionally substituted alkenyl, and optionally substituted alkynyl;

R_4 is H; or R_4 is of Formula (i):



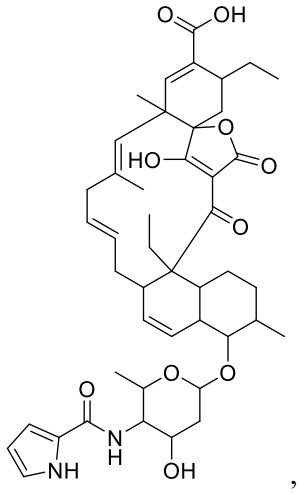
Formula (i)

wherein * represents the point of attachment to Formula (I); and

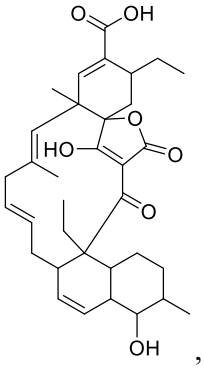
R_a, R_b, and R_c are independently selected from the group consisting of H, halogen, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl; and

R_d is H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl.

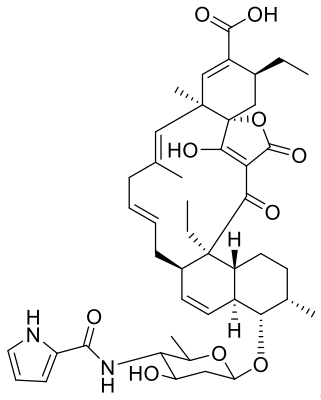
In another aspect of the present disclosure, there is provided a compound as disclosed herein, or a compound selected from the group consisting of:



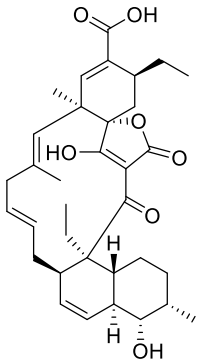
Compound 8'



Compound 9'



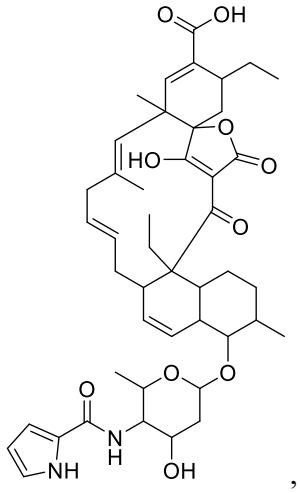
Compound 8



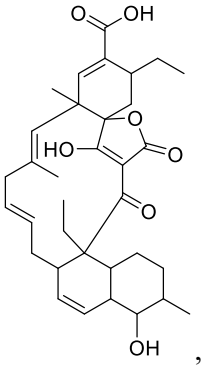
Compound 9,

or a pharmaceutically acceptable salt, or stereoisomer thereof, for use in therapy.

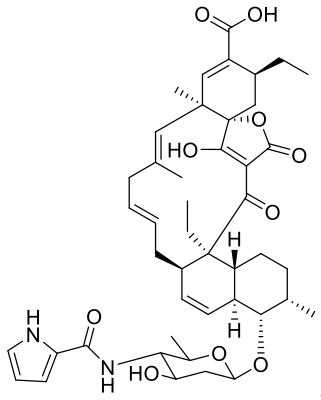
In another aspect of the present disclosure, there is provided use of a compound as disclosed herein, or a compound selected from the group consisting of:



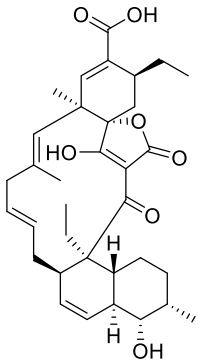
Compound 8'



Compound 9'



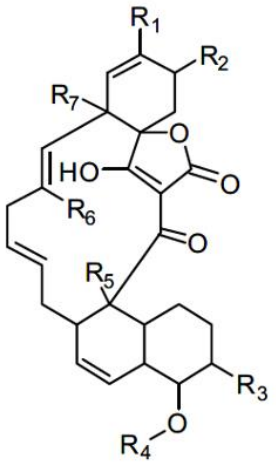
Compound 8



Compound 9,

or a pharmaceutically acceptable salt, or stereoisomer thereof, in the manufacture of a medicament for treating a bacterial infection.

There is provided a method of isolating a compound of Formula (I),



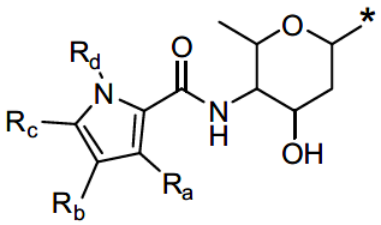
Formula (I)

wherein:

R_1 is -COOH, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl;

R_2, R_3, R_5, R_6 and R_7 are independently selected from the group consisting of H, optionally substituted alkyl, optionally substituted alkenyl, and optionally substituted alkynyl;

R_4 is H; or R_4 is of Formula (i):



Formula (i)

wherein * represents the point of attachment to Formula (I); and

R_a, R_b, and R_c are independently selected from the group consisting of H, halogen, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl; and

R_d is H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl;

the method comprising:

(i) expanding an *Actinomadura* sp. strain under culture conditions that allow expansion of the strain to obtain a seed culture;

(ii) using the seed culture to inoculate a fermentation culture;

(iii) incubating the fermentation culture; and
(iv) isolating the compound from the fermentation culture.

In another aspect of the present disclosure, there is provided a method of isolating a compound as disclosed herein, the method comprising:

(i) expanding an *Actinomadura* sp. strain under culture conditions that allow expansion of the strain to obtain a seed culture;
(ii) using the seed culture to inoculate a fermentation culture;
(iii) incubating the fermentation culture; and
(iv) isolating the compound from the fermentation culture.

Definitions

Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, chemistry described herein, are those well-known and commonly used in the art.

Unless otherwise indicated, compounds disclosed and/or described herein include all possible enantiomers, diastereomers, meso isomers and other stereoisomeric forms, including racemic mixtures, optically pure forms and intermediate mixtures thereof. Enantiomers, diastereomers, meso isomers and other stereoisomeric forms may be prepared using chiral synthons or reagents, or resolved using conventional techniques. Unless specified otherwise, when the compounds disclosed and/or described herein contain olefinic double bonds or other centers of geometric asymmetry, it is intended that the compounds include both E and Z isomers. When the compounds described herein contain moieties capable of tautomerization, and unless specified otherwise, it is intended that the compounds include all possible tautomers.

As used herein, the term “isomers” refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

As used here, the term “tautomer” refers to one of two or more structural isomers that exist in equilibrium and which are readily converted from one isomeric form to another. It will be apparent to one skilled in the art that certain compounds of this disclosure may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the disclosure.

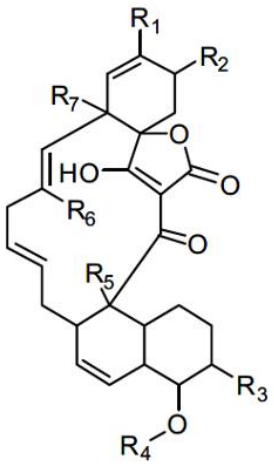
As used herein, the term “congener” refers to compounds that may be related to each other by origin, structure, or function.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the disclosure.

As used herein, the term "alkyl" includes within its meaning monovalent (“alkyl”) and divalent (“alkylene”) straight chain or branched chain saturated aliphatic groups having from 1 to 12 carbon atoms, eg, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms. For example, the term alkyl includes, but is not limited to, methyl, ethyl, 1-propyl, isopropyl, 1-butyl, 2-butyl, isobutyl, tert-butyl, amyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, pentyl, isopentyl, hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, 2-ethylpentyl, 3-ethylpentyl, heptyl, 1-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, 5-methylheptyl, 1-methylheptyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. Alkyl groups may be optionally substituted.

CLAIMS

1. A compound of Formula (I) or a pharmaceutically acceptable salt, or stereoisomer thereof:



Formula (I)

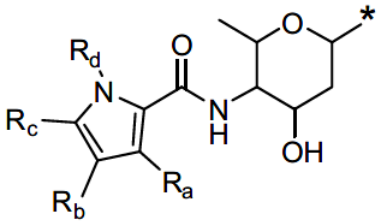
wherein:

R_2, R_3, R_5, R_6 and R_7 are independently selected from the group consisting of H, optionally substituted alkyl, optionally substituted alkenyl, and optionally substituted alkynyl;

R_1 is -COOH when R_6 is H;

R_1 is optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl when R_6 is optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl;

R_4 is H or of Formula (i):



Formula (i)

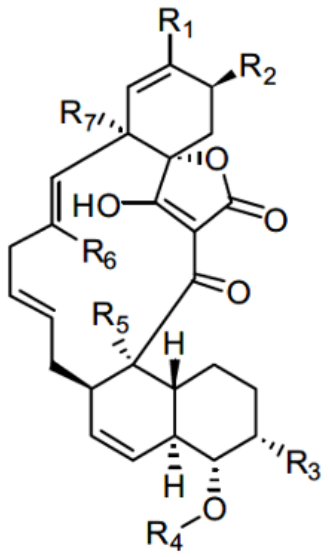
wherein * represents the point of attachment to Formula (I);

R_d is H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl;

R_a, R_b, R_c are halogen.

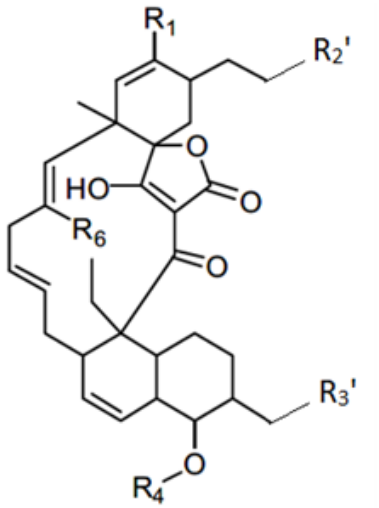
2. The compound of claim 1, wherein R_4 and R_6 are not both H at the same time.

3. The compound of claim 1 or 2, wherein the compound has the structure and stereochemical configuration of Formula (II):



Formula (II)

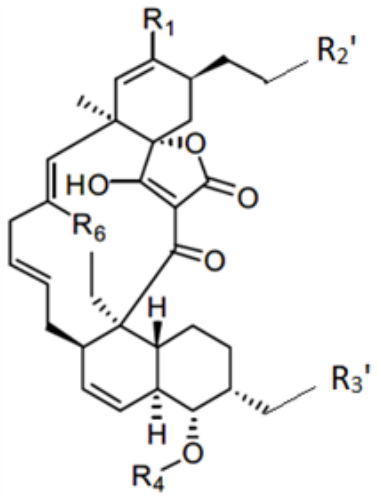
4. The compound of any one of claims 1 to 3, wherein the compound is of Formula (III):



Formula (III)

wherein R_2' and R_3' are independently H or -CH_3.

5. The compound of any one of claims 1 to 4, wherein the compound has the structure and stereochemical configuration of Formula (IV):



Formula (IV)

wherein R_2' and R_3' are independently H or -CH_3.

6. The compound of any one of claims 1 to 5, wherein R_1 is -COOH or optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, or optionally substituted C_{2-6} alkynyl.

7. The compound of any one of claims 1 to 6, wherein R_1 is -COOH, methyl, ethyl, propyl, *n*-propyl, isopropyl, butyl, *n*-butyl, *sec*-butyl, isobutyl, or *tert*-butyl.

8. The compound of any one of claims 1 to 7, wherein R_2 is optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, or optionally substituted C_{2-6} alkynyl.

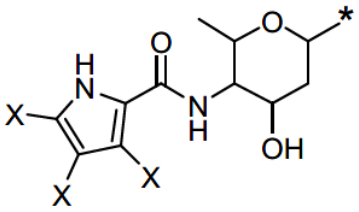
9. The compound of any one of claims 1 to 8, wherein R_2 is methyl, ethyl, propyl, *n*-propyl, isopropyl, butyl, *n*-butyl, *sec*-butyl, isobutyl, or *tert*-butyl.

10. The compound of any one of claims 1 to 9, wherein R_3 is optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, or optionally substituted C_{2-6} alkynyl.

11. The compound of any one of claims 1 to 10, wherein R_3 is methyl, ethyl, propyl, *n*-propyl, isopropyl, butyl, *n*-butyl, *sec*-butyl, isobutyl, or *tert*-butyl.

12. The compound of any one of claims 1 to 11, wherein R_4 is H.

13. The compound of any one of claims 1 to 11, wherein R_4 is of Formula (ii):



Formula (ii)

wherein X is halogen.

14. The compound of claim 13, wherein X is F, Cl, Br or I.

15. The compound of claim 13 or 14, wherein X is Cl.

16. The compound of any one of claims 1 to 15, wherein R_d is H, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, or optionally substituted C_{2-6} alkynyl.

17. The compound of any one of claims 1 to 16, wherein R_d is H, methyl, ethyl, propyl, *n*-propyl, isopropyl, butyl, *n*-butyl, *sec*-butyl, isobutyl, or *tert*-butyl.

18. The compound of any one of claims 1 to 17, wherein R_5 is optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, or optionally substituted C_{2-6} alkynyl.

19. The compound of any one of claims 1 to 18, wherein R_5 is methyl, ethyl, propyl, *n*-propyl, isopropyl, butyl, *n*-butyl, *sec*-butyl, isobutyl, or *tert*-butyl.

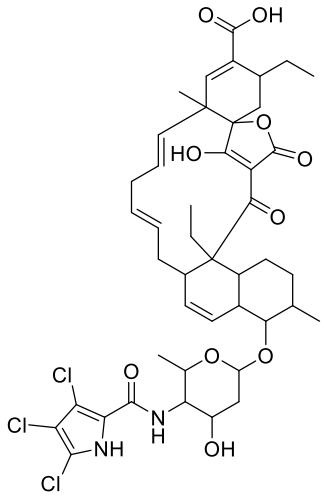
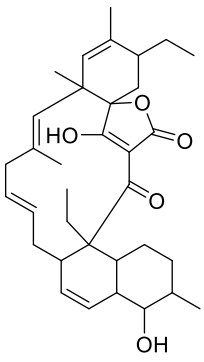
20. The compound of any one of claims 1 to 19, wherein (i) R_4 is of Formula (i) and R_6 is H, or (ii) R_4 is H and R_6 is optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, or optionally substituted C_{2-6} alkynyl.

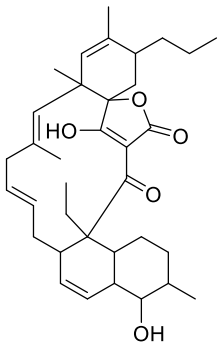
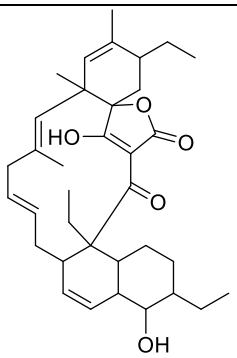
21. The compound of any one of claims 1 to 20, wherein (i) R_4 is of Formula (i) and R_6 is H, or (ii) R_4 is H and R_6 is methyl, ethyl, propyl, *n*-propyl, isopropyl, butyl, *n*-butyl, *sec*-butyl, isobutyl, or *tert*-butyl.

22. The compound of any one of claims 1 to 21, wherein R_7 is optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, or optionally substituted C_{2-6} alkynyl.

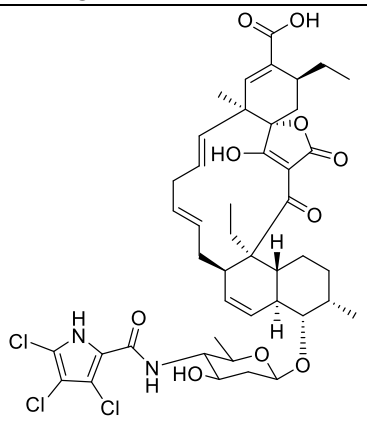
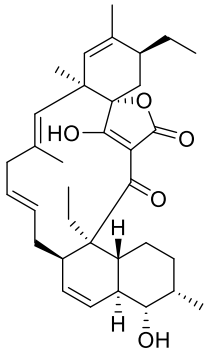
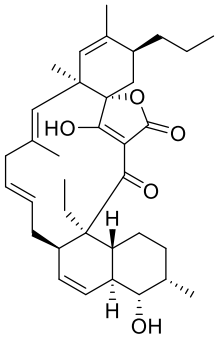
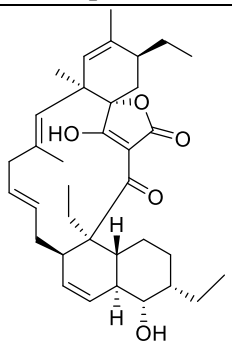
23. The compound of any one of claims 1 to 22, wherein R_7 is methyl, ethyl, propyl, *n*-propyl, isopropyl, butyl, *n*-butyl, *sec*-butyl, isobutyl, or *tert*-butyl.

24. The compound of any one of claims 1 to 23, wherein the compound is selected from the group consisting of:

 **Compound 7'**	 **Compound 10'**

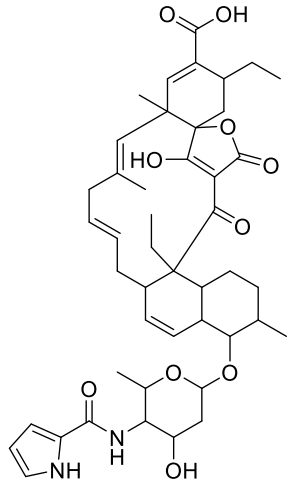
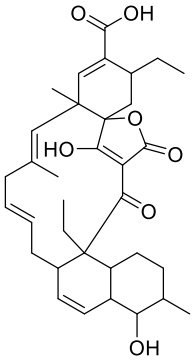
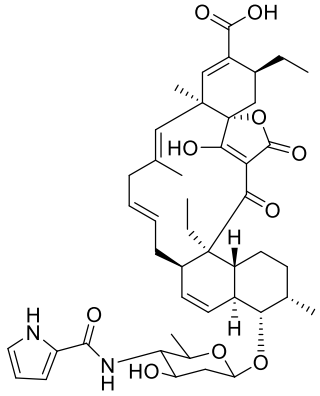
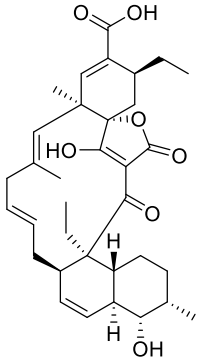
 **Compound 11'**	 **Compound 12'.**

25. The compound of any one of claims 1 to 24, wherein the compound is selected from the group consisting of:

 **Compound 7**	 **Compound 10**
 **Compound 11**	 **Compound 12.**

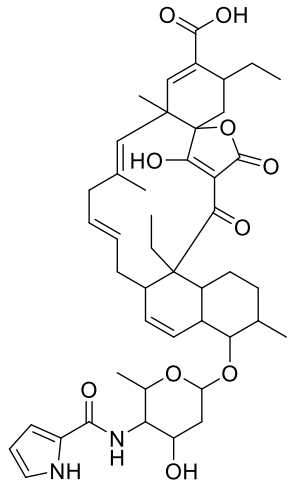
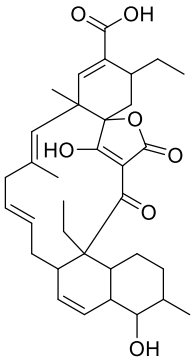
26. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1 to 25, or a pharmaceutically acceptable salt, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

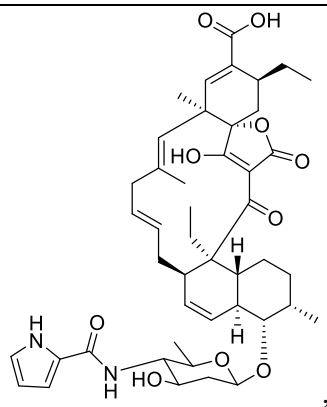
27. A compound of any one of claims 1 to 25, or a compound selected from the group consisting of:

 , **Compound 8'**	 , **Compound 9'**
 , and **Compound 8**	 **Compound 9**,

or a pharmaceutically acceptable salt, or stereoisomer thereof, for use in therapy.

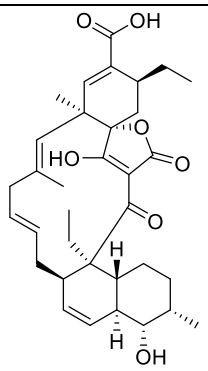
28. Use of a compound of any one of claims 1 to 25, or a compound selected from the group consisting of:

 , **Compound 8'**	 , **Compound 9'**



, and

Compound 8



Compound 9,

or a pharmaceutically acceptable salt, or stereoisomer thereof, in the manufacture of a medicament for treating a bacterial infection.

29. The use of claim 28, wherein the infection is a *Staphylococcus*, *Bacillus*, *Clostridium*, *Acinetobacter*, *Klebsiella*, or *Pseudomonas* infection.

30. The use of claim 28 or 29, wherein the infection is caused by *Staphylococcus aureus*, *Staphylococcus aureus* Rosenbach, gram-positive methicillin-resistant *Staphylococcus aureus* (MRSA), *Bacillus cereus*, *Bacillus subtilis*, *Clostridium perfringens*, *Acinetobacter baumannii*, *Klebsiella aerogenes*, or *Pseudomonas aeruginosa*.

31. A method of isolating a compound of any one of claims 1-25, the method comprising:

    (i) expanding an *Actinomadura* sp. strain under culture conditions that allow expansion of the strain to obtain a seed culture;
    (ii) using the seed culture to inoculate a fermentation culture;
    (iii) incubating the fermentation culture; and
    (iv) isolating the compound from the fermentation culture.

32. The method of claim 31, wherein step (iii) comprises incubating the fermentation culture for 7 to 12 days.

33. The method of claim 31 or 32, wherein step (iii) comprises incubating the fermentation culture at a temperature of 25°C to 35°C.

34. The method of any one of claims 31 to 33, wherein step (iii) comprises incubating the fermentation culture with a shaking condition of 150 to 350 rpm.

35. The method of any one of claims 31 to 34, wherein step (iii) comprises incubating the fermentation culture for 9 days at 28 °C with shaking condition of 200 rpm.

36. The method of any one of claims 31 to 35, wherein the compound is isolated using a method selected from the group consisting of centrifugation, precipitation, filtration, liquid extraction, methanol extraction, chromatography, column chromatography, affinity chromatography, evaporation, lyophilization, and combinations thereof.