ala-D-ala termini of Lipid II molecules and/or to nascent peptidoglycan, preventing maturation of the cell wall. Vancomycin is used to treat infections that are resistant to antibiotics, including antibiotic-resistance *S. aureus* infections. Hence, vancomycin has been called the "antibiotic of last resort" because it is often the last remaining option for the treatment of Gram-positive infections caused by strains that have become resistant to all other antibiotics. Resistance to vancomycin first appeared about fifteen years ago and the frequency of resistance is increasing. There have been numerous efforts to develop further treatments to combat the emergent vancomycin-resistant strains.

[00010] Thus, there exists a strong unmet need for developing effective antibiotics in order to combat the growing problem of antibiotic-resistant bacteria, including antibiotic-resistant *S. aureus* strains. There also exists a need of enhancing efficacy of vancomycin and other existing antibiotics.

[00011] The foregoing discussion is presented solely to provide a better understanding of the nature of the problems confronting the art and should not be construed in any way as an admission as to prior art nor should the citation of any reference herein be construed as an admission that such reference constitutes "prior art" to the instant application.

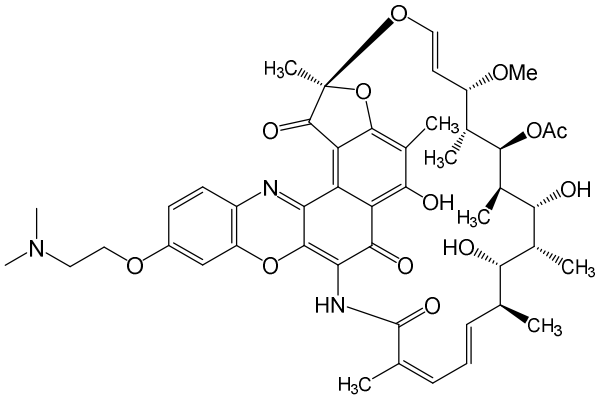
SUMMARY OF THE DISCLOSURE

[00012] As discussed herein, there is a strong need to develop effective treatments for bacterial infections in general and *S. aureus* infections in particular. The present disclosure addresses these and other needs by providing combinations of rifamycin analog compounds and vancomycin, as well as pharmaceutical compositions and dosage forms comprising same, and methods of treatment based on such compounds and pharmaceutical compositions.

[00013] Various non-limiting examples are described below.

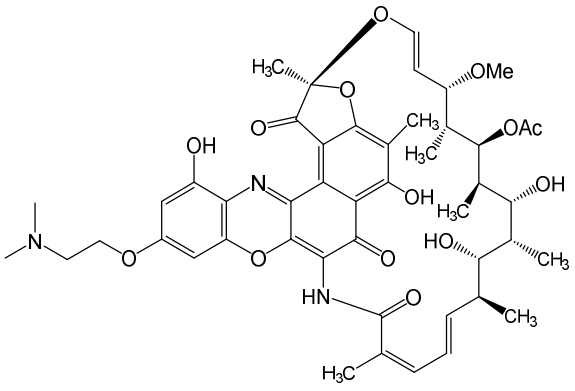
[00013a] In one aspect, the present disclosure provides a use of an effective amount of:

a) a compound selected from



(I)

and

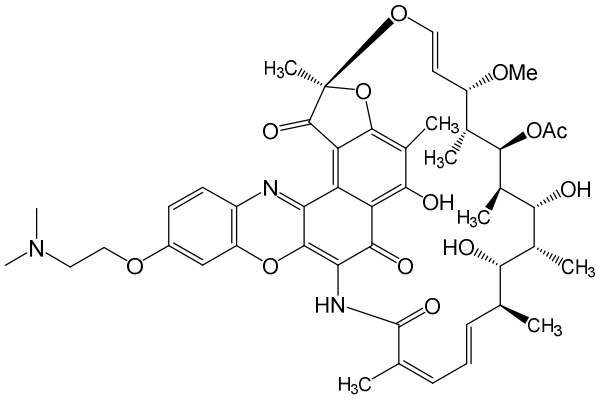


(II), or a pharmaceutically acceptable salt thereof, and

b) vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for preventing or inhibiting growth of a bacterium.

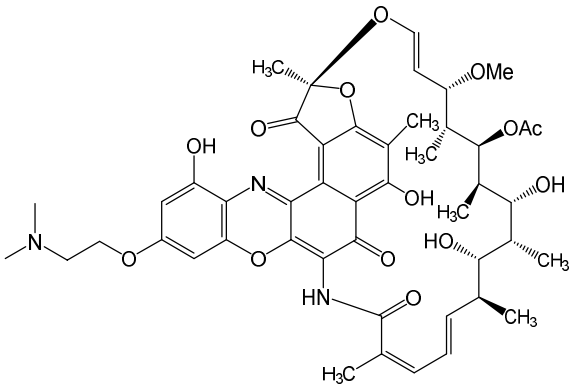
[00014] In one example, the present disclosure provides a method of preventing or inhibiting growth of a bacterium comprising administering an effective amount of:

a) a compound selected from



(I)

and



(II), or a pharmaceutically acceptable salt thereof, and

b) vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof.

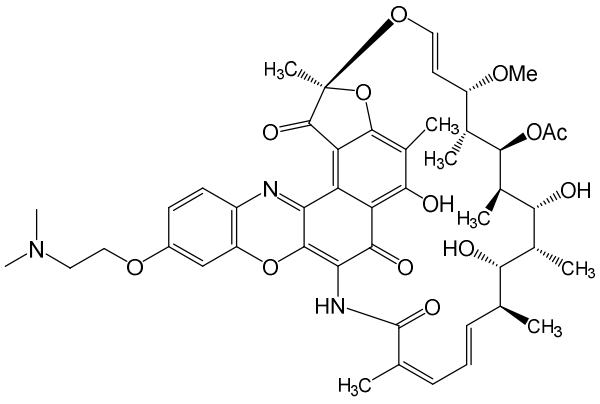
[00015] In one example, the compound of a) is compound (I) or a pharmaceutically acceptable salt thereof. In one example, the compound of a) is compound (II) or a pharmaceutically acceptable salt thereof.

[00016] In one example, the bacterium is a Gram-positive bacterium. In one example, the bacterium is a penicillin-resistant bacterium, or a methicillin-resistant bacterium.

[00017] In one example, the bacterium is *Staphylococcus aureus*. In one example, the bacterium is selected from methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *Staphylococcus aureus* (MSSA). In one example, the bacterium is methicillin-resistant *Staphylococcus aureus* (MRSA).

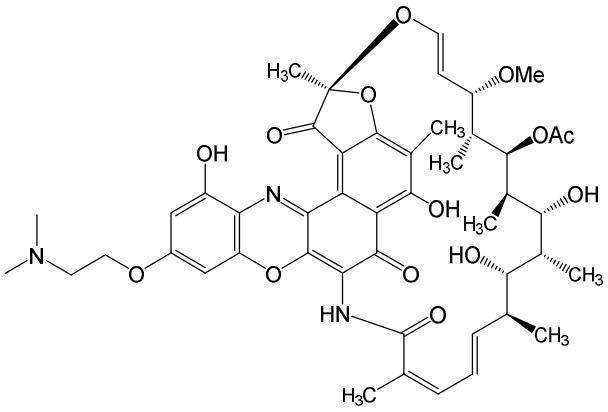
[00017a] In another aspect, the present disclosure provides a use of an effective amount of:

a) a compound selected from



(I)

and

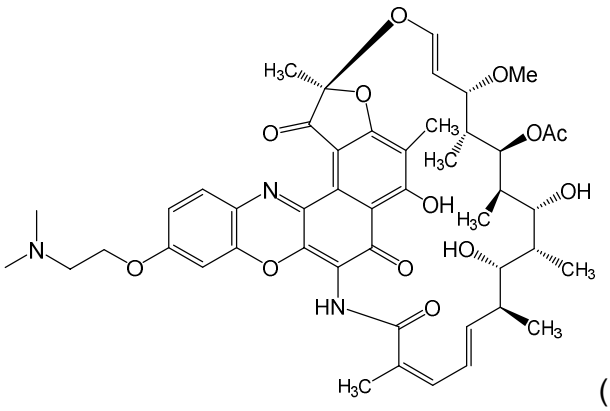


(II), or a pharmaceutically acceptable salt thereof, and

b) vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a bacterial infection in a subject in need of such treatment.

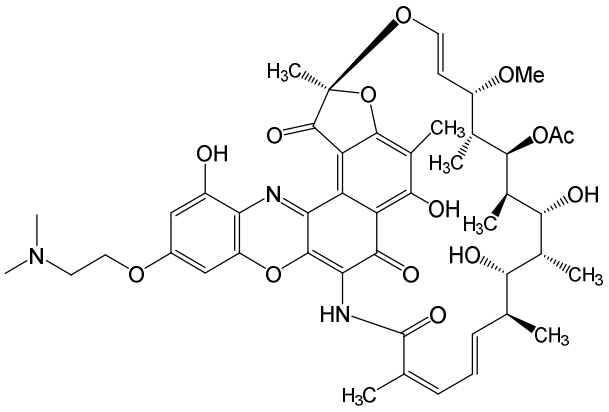
[00018] In another example, the present disclosure provides a method of treating a bacterial infection in a subject in need of such treatment comprising administering to the subject an effective amount of:

a) a compound selected from



(I)

and



(II), or a pharmaceutically acceptable salt thereof, and

b) vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof.

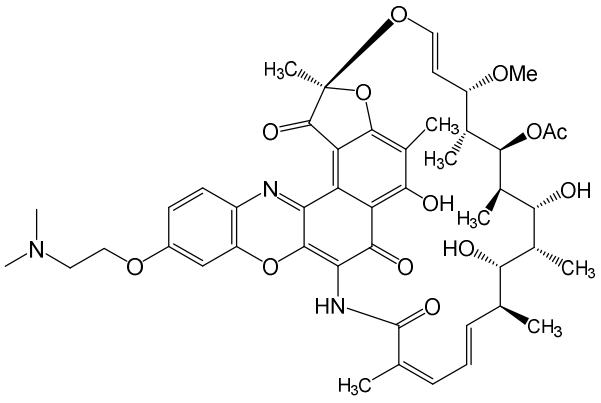
[00019] In one example, the compound of a) is compound (I) or a pharmaceutically acceptable salt thereof. In one example, the compound of a) is compound (II) or a pharmaceutically acceptable salt thereof.

[00020] In one example, the bacterial infection is caused by a Gram-positive bacterium. In one example, the bacterial infection is caused by a penicillin-resistant bacterium or a methicillin-resistant bacterium.

[00021] In one example, wherein the bacterial infection is caused by *Staphylococcus aureus*. In one example, the bacterial infection is caused by a bacterium selected from methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *Staphylococcus aureus* (MSSA). In one example, the bacterial infection is caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

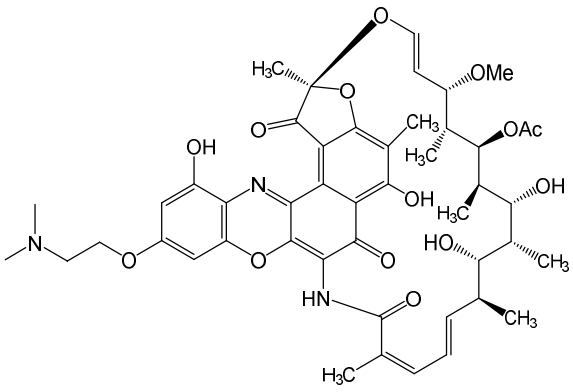
[00022] In one example, the bacterial infection is selected from cellulitis, bacteremia, dermonecrosis, eyelid infection, eye infection, neonatal conjunctivitis, osteomyelitis, impetigo, boils, scalded skin syndrome, food poisoning, pneumonia, surgical infection, urinary tract infection, burn infection, meningitis, endocarditis, septicemia, toxic shock syndrome, septic arthritis, mastitis, infection associated with a prosthetic joint, infection associated with a catheter, and infection associated with an implant.

[00022a] In another aspect, the present disclosure provides a use of an effective amount of a) a compound selected from



(I)

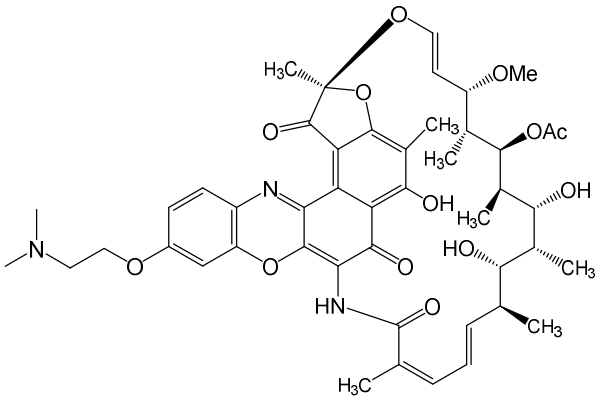
and



(II), or a pharmaceutically acceptable salt thereof, and

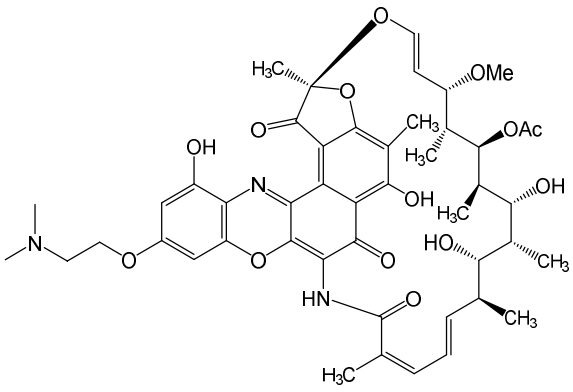
b) vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for preventing or treating a disease in a subject, wherein the disease is selected from cellulitis, bacteremia, dermonecrosis, eyelid infection, eye infection, neonatal conjunctivitis, osteomyelitis, impetigo, boils, scalded skin syndrome, food poisoning, pneumonia, surgical infection, urinary tract infection, burn infection, meningitis, endocarditis, septicemia, toxic shock syndrome, septic arthritis, mastitis, infection associated with a prosthetic joint, infection associated with a catheter, and infection associated with an implant.

[00023] In another example, the present disclosure provides a method of preventing or treating a disease in a subject in need thereof comprising administering to the subject an effective amount of a) a compound selected from



(I)

and



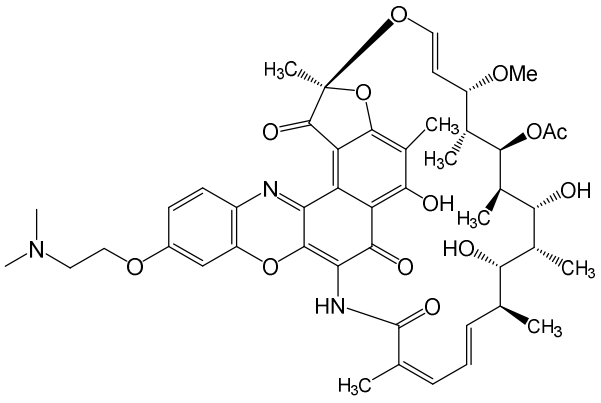
(II), or a pharmaceutically acceptable salt thereof, and

b) vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof,

wherein the disease is selected from cellulitis, bacteremia, dermonecrosis, eyelid infection, eye infection, neonatal conjunctivitis, osteomyelitis, impetigo, boils, scalded skin syndrome, food poisoning, pneumonia, surgical infection, urinary tract infection, burn infection, meningitis, endocarditis, septicemia, toxic shock syndrome, septic arthritis, mastitis, infection associated with a prosthetic joint, infection associated with a catheter, and infection associated with an implant.

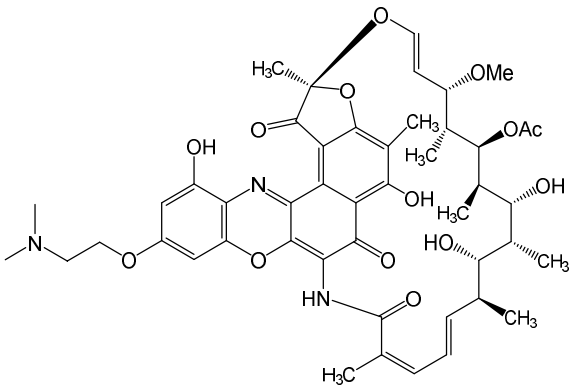
[00023a] In another aspect, the present disclosure provides a use of an effective amount of:

a) a compound selected from



(I)

and

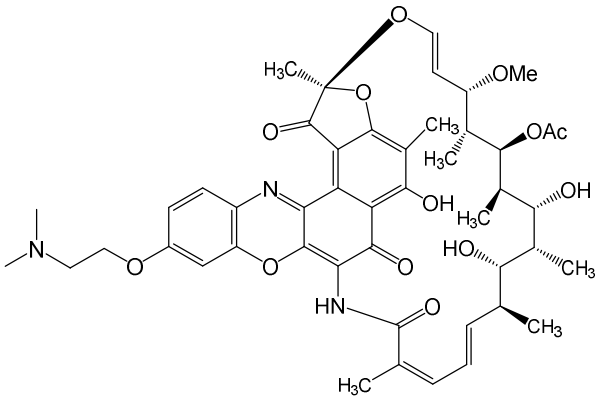


(II), or a pharmaceutically acceptable salt thereof, in combination with

b) vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for enhancing efficacy of vancomycin or a derivative thereof.

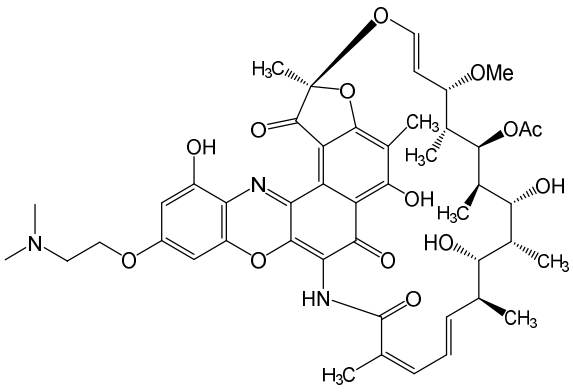
[00024] In another example, the present disclosure provides a method of enhancing efficacy of vancomycin or a derivative thereof comprising administering to a subject in need thereof an effective amount of:

a) a compound selected from



(I)

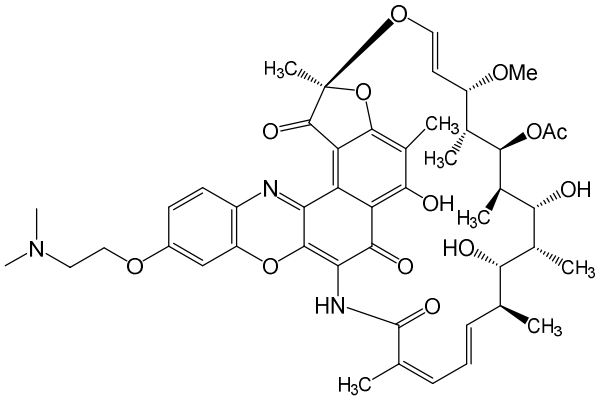
and



(II), or a pharmaceutically acceptable salt thereof, in combination with

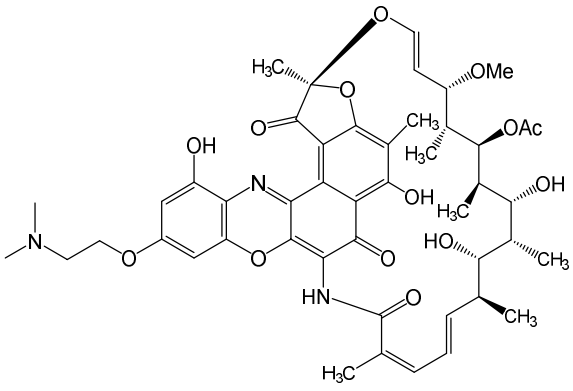
b) vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof.

[00024a] In another aspect, the present disclosure provides a use of an effective amount of a compound



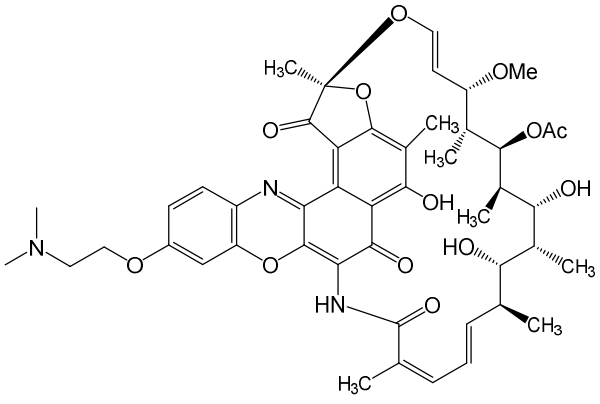
(I)

or



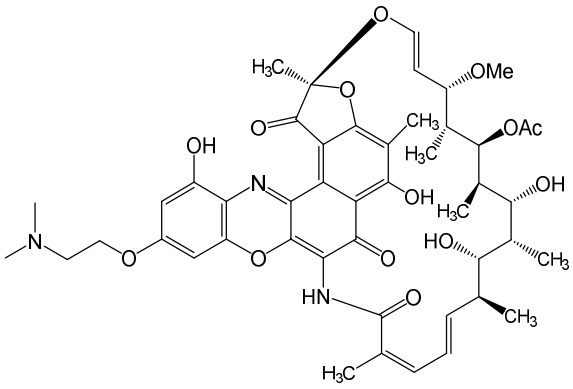
(II), in combination with vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for enhancing efficacy of the compound selected from (I) and (II), or a pharmaceutically acceptable salt thereof.

[00025] In yet another example, the present disclosure provides a method of enhancing efficacy of a compound selected from



(I)

and



(II), or a pharmaceutically acceptable salt thereof, the method comprising administering a subject in need thereof an effective amount of the compound (I) or (II) in combination with vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof.

[00026] In one example, the compound (I) or (II), or a pharmaceutically acceptable salt thereof, is administered orally, subcutaneously, or intravenously. In one example, the vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, is administered orally, subcutaneously, or intravenously.

[00027] In one example, the compound (I) or (II), or a pharmaceutically acceptable salt thereof, and the vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, are administered in a single dosage form. In one example, the compound (I) or (II), or a pharmaceutically acceptable salt thereof, and the vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, are administered in separate dosage forms.

[00028] In one example, the compound (I) or (II), or a pharmaceutically acceptable salt thereof, and the vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, are administered on the same day. In one example, the compound (I) or (II), or a pharmaceutically acceptable salt thereof, and the vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, are administered simultaneously.

[00029] In one example, the compound (I) or (II), or a pharmaceutically acceptable salt thereof, and the vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, are not administered on the same day. In one example, the compound (I) or (II), or a pharmaceutically acceptable salt thereof, and the vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, are administered on consecutive days.

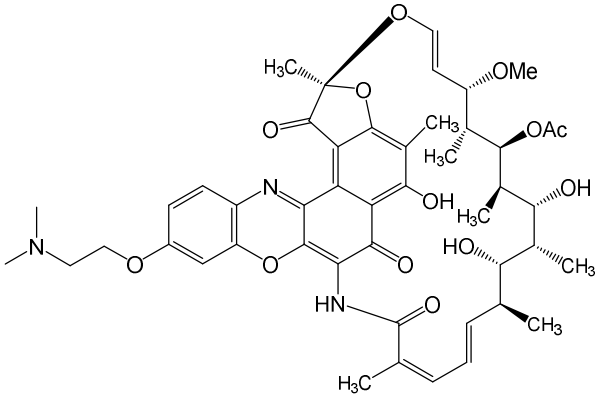
[00030] In one example, the compound (I) or (II), or a pharmaceutically acceptable salt thereof, and the vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, are administered on separate, non-consecutive days.

[00031] In one example, the vancomycin or a derivative thereof, or a pharmaceutically

acceptable salt thereof, is administered twice daily. In one example, the compound (I) or (II), or a pharmaceutically acceptable salt thereof, is administered once daily.

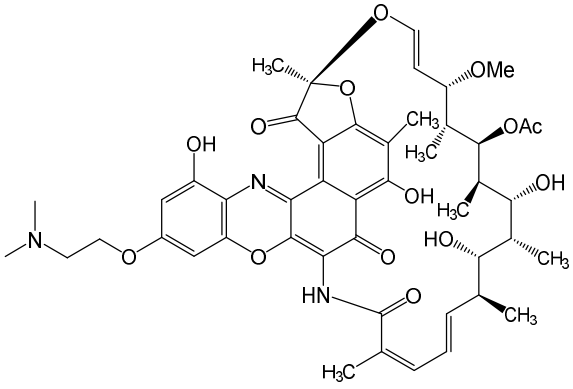
[00032] In one example, the subject is human.

[00033] In another aspect, the present disclosure provides a pharmaceutical composition comprising a) a compound selected from



(I)

and



(II), or a pharmaceutically acceptable salt thereof,

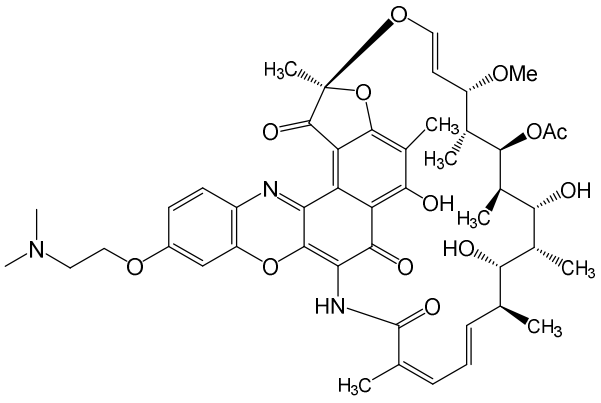
b) vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, and

c) a pharmaceutically acceptable carrier.

[00034] In one example, the pharmaceutical composition comprises from about 0.01 mg to about 5000 mg of vancomycin or a derivative thereof.

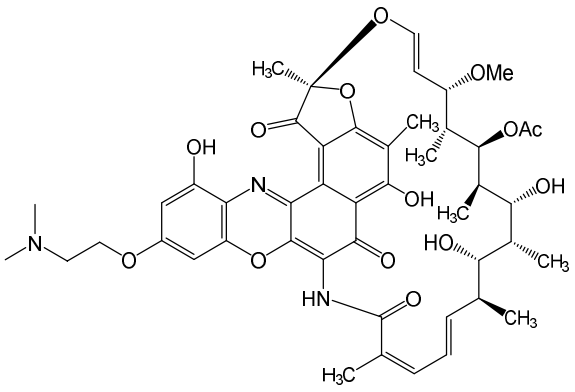
[00035] In one example, the pharmaceutical composition comprises from about 0.001 mg to about 5000 mg of the compound (I) or (II). In one example, the pharmaceutical composition comprises from about 0.01 mg to about 500 mg of the compound (I) or (II).

[00036] In another aspect, the present disclosure provides a pharmaceutical dosage form comprising a) a compound selected from



(I)

and



(II), or a pharmaceutically acceptable salt thereof,

b) vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, and

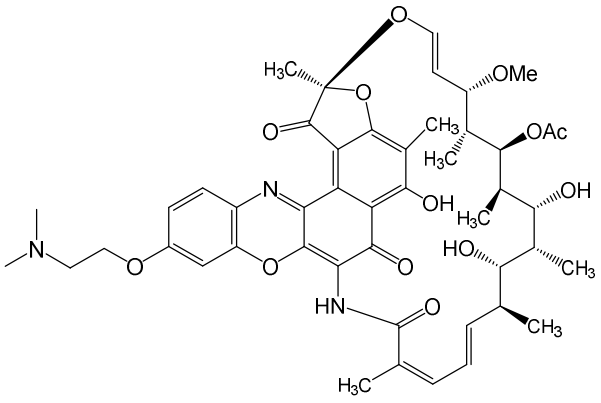
c) a pharmaceutically acceptable vehicle.

[00037] In one example, the pharmaceutical dosage form comprises the dosage form is an oral dosage form or an injectable dosage form.

[00038] In one example, the pharmaceutical dosage form comprises from about 0.01 mg to about 5000 mg of vancomycin or a derivative thereof. In one example, the pharmaceutical dosage form comprises from about 0.001 mg to about 5000 mg of the compound (I) or (II). In one example, the pharmaceutical dosage form comprises from about 0.01 mg to about 500 mg of the compound (I) or (II).

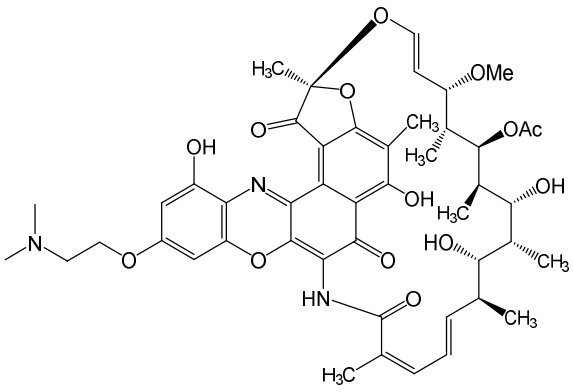
[00039] In one example, the pharmaceutical dosage form is formulated for a single administration. In one example, the pharmaceutical dosage form is formulated for multiple administrations.

[00040] In yet another aspect, the present disclosure provides a kit comprising a) a first container comprising a compound selected from



(I)

and



(II), or a pharmaceutically acceptable salt thereof,

b) a second container comprising vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, and

c) instructions for administration of the compound (I) or (II) and the vancomycin or a derivative thereof.

[00041] In one example, the first container comprises compound (I) or a pharmaceutically acceptable salt thereof. In one example, the first container comprises compound (II) or a pharmaceutically acceptable salt thereof.

[00042] These and other examples of the present disclosure will become apparent to those skilled in the art after a reading of the following detailed description of the disclosure, including the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

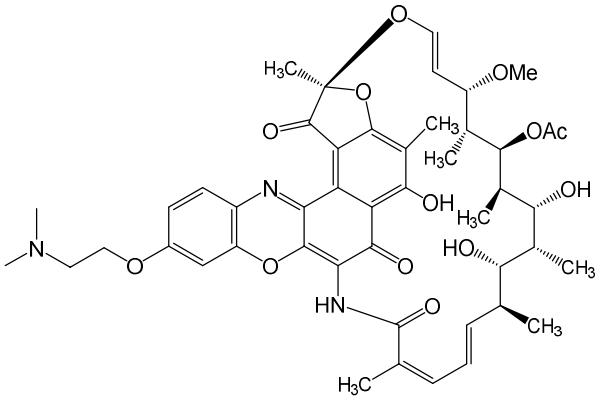
[00043] **Figure 1** is a bar graph of the median *S. aureus* NRS384 kidney burden in mice treated with rifampicin in combination with vancomycin.

[00044] **Figure 2** is a bar graph of the median *S. aureus* NRS384 kidney burden in mice treated with rifamycin analogs (I) and (II) according to the disclosure in combination with

WHAT IS CLAIMED IS:

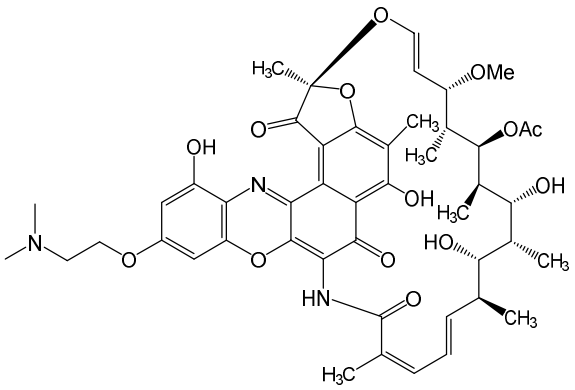
1. Use of an effective amount of:

   a) a compound selected from



(I)

   and



(II), or a pharmaceutically acceptable salt thereof, and

   b) vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for preventing or inhibiting growth of a bacterium.

2. The use of claim 1, wherein the compound of a) is compound (I) or a pharmaceutically acceptable salt thereof.

3. The use of claim 1, wherein the compound of a) is compound (II) or a pharmaceutically acceptable salt thereof.

4. The use of any one of claims 1-3, wherein the bacterium is a Gram-positive bacterium.

5. The use of any one of claims 1-4, wherein the bacterium is a penicillin-resistant bacterium,

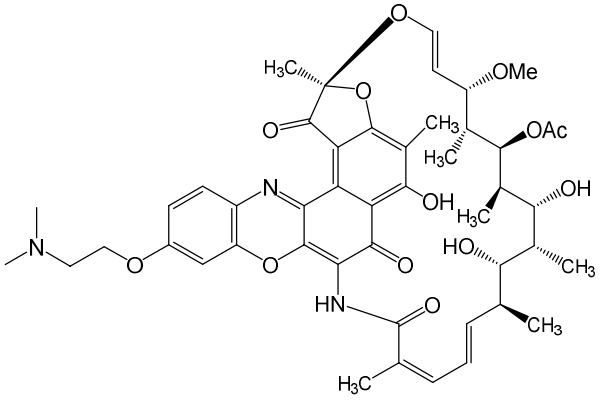
or a methicillin-resistant bacterium.

6. The use of any one of claims 1-5, wherein the bacterium is Staphylococcus aureus.

7. The use of any one of claims 1-6, wherein the bacterium is selected from methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-susceptible Staphylococcus aureus (MSSA).

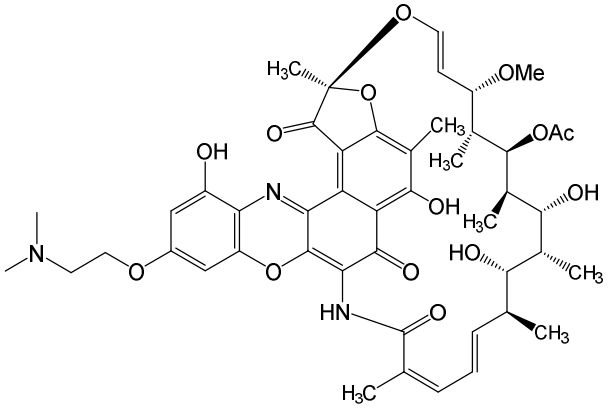
8. The use of any one of claims 1-7, wherein the bacterium is methicillin-resistant Staphylococcus aureus (MRSA).

9. Use of an effective amount of:
a) a compound selected from



(I)

and



(II), or a pharmaceutically acceptable salt thereof, and

b) vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a bacterial infection in a subject in need of such treatment.

10. The use of claim 9, wherein the compound of a) is compound (I) or a pharmaceutically acceptable salt thereof.

11. The use of claim 9, wherein the compound of a) is compound (II) or a pharmaceutically acceptable salt thereof.

12. The use of any one of claims 9-11, wherein the bacterial infection is caused by a Gram-positive bacterium.

13. The use of any one of claims 9-12, wherein the bacterial infection is caused by a penicillin-resistant bacterium or a methicillin-resistant bacterium.

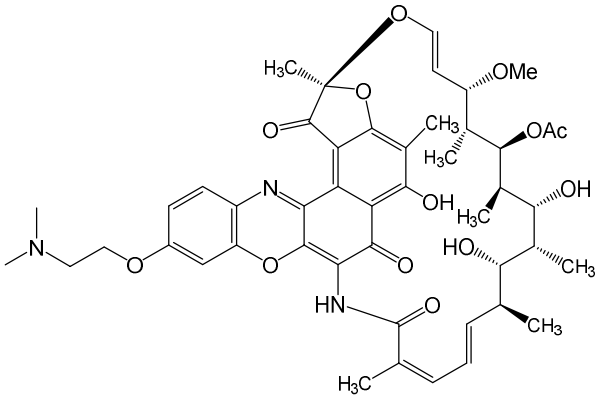
14. The use of any one of claims 9-13, wherein the bacterial infection is caused by Staphylococcus aureus.

15. The use of any one of claims 9-14, wherein the bacterial infection is caused by a bacterium selected from methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-susceptible Staphylococcus aureus (MSSA).

16. The use of any one of claims 9-15, wherein the bacterial infection is caused by methicillin-resistant Staphylococcus aureus (MRSA).

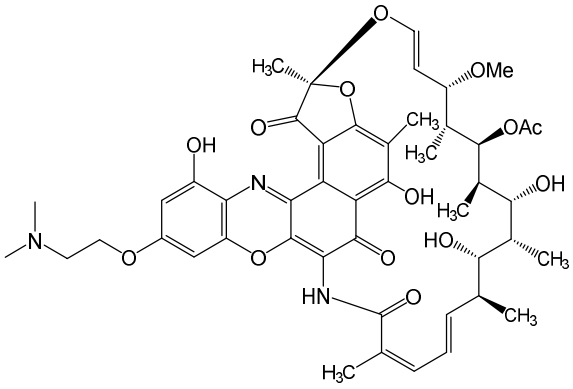
17. The use of any of claims 9-16, wherein the bacterial infection is selected from cellulitis, bacteremia, dermonecrosis, eyelid infection, eye infection, neonatal conjunctivitis, osteomyelitis, impetigo, boils, scalded skin syndrome, food poisoning, pneumonia, surgical infection, urinary tract infection, burn infection, meningitis, endocarditis, septicemia, toxic shock syndrome, septic arthritis, mastitis, infection associated with a prosthetic joint, infection associated with a catheter, and infection associated with an implant.

18. Use of an effective amount of a) a compound selected from



(I)

and

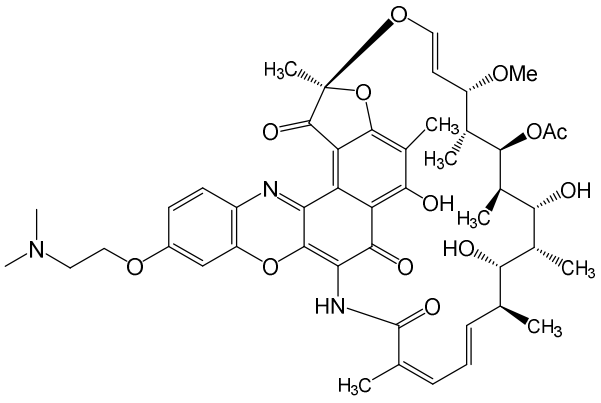


(II), or a pharmaceutically acceptable salt thereof, and

b) vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for preventing or treating a disease in a subject, wherein the disease is selected from cellulitis, bacteremia, dermonecrosis, eyelid infection, eye infection, neonatal conjunctivitis, osteomyelitis, impetigo, boils, scalded skin syndrome, food poisoning, pneumonia, surgical infection, urinary tract infection, burn infection, meningitis, endocarditis, septicemia, toxic shock syndrome, septic arthritis, mastitis, infection associated with a prosthetic joint, infection associated with a catheter, and infection associated with an implant.

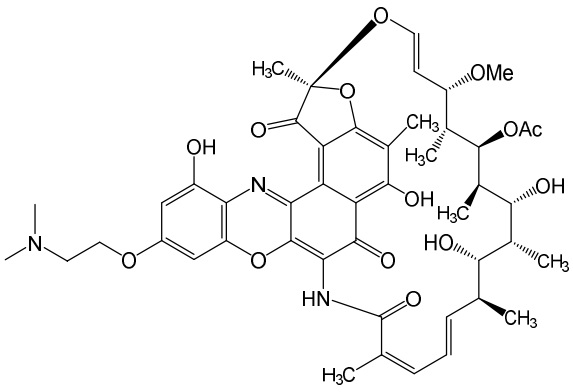
19. Use of an effective amount of:

a) a compound selected from



(I)

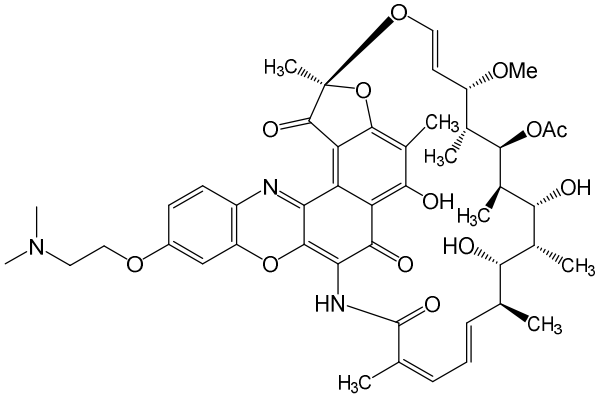
and



(II), or a pharmaceutically acceptable salt thereof, in combination with

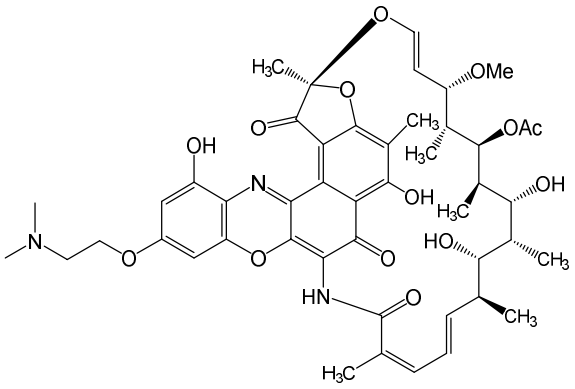
b) vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for enhancing efficacy of vancomycin or a derivative thereof.

20. Use of an effective amount of a compound



(I)

or



(II), in combination with vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for enhancing efficacy of the compound selected from (I) and (II), or a pharmaceutically acceptable salt thereof.

21. The use of any one of claims 1-20, wherein the compound (I) or (II), or a pharmaceutically acceptable salt thereof, is to be administered orally, subcutaneously, or intravenously.

22. The use of any one of claims 1-21, wherein the vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, is to be administered orally, subcutaneously, or intravenously.

23. The use of any one of claims 1-22, wherein the compound (I) or (II), or a pharmaceutically acceptable salt thereof, and the vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, are to be administered in a single dosage form.

24. The use of any one of claims 1-22, wherein the compound (I) or (II), or a pharmaceutically acceptable salt thereof, and the vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, are to be administered in separate dosage forms.

25. The use of any one of claims 1-24, wherein the compound (I) or (II), or a pharmaceutically acceptable salt thereof, and the vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, are to be administered on the same day.

26. The use of any one of claims 1-25, wherein the compound (I) or (II), or a pharmaceutically acceptable salt thereof, and the vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, are to be administered simultaneously.

27. The use of any one of claims 1-22, wherein the compound (I) or (II), or a pharmaceutically acceptable salt thereof, and the vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, are not to be administered on the same day.

28. The use of claim 27, wherein the compound (I) or (II), or a pharmaceutically acceptable salt thereof, and the vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, are to be administered on consecutive days.

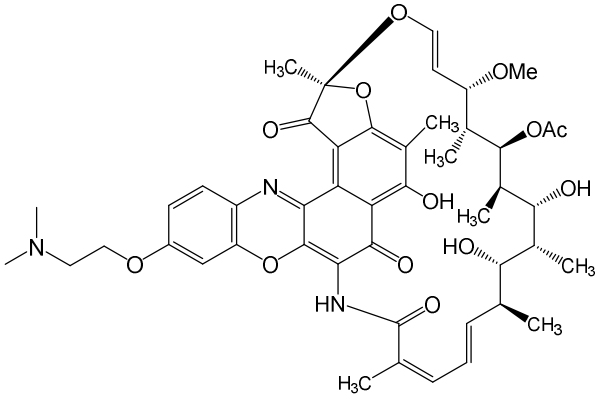
29. The use of claim 28, wherein the compound (I) or (II), or a pharmaceutically acceptable salt thereof, and the vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, are to be administered on separate, non-consecutive days.

30. The use of any one of claims 1-29, wherein the vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, is to be administered twice daily.

31. The use of any one of claims 1-29, wherein the compound (I) or (II), or a pharmaceutically acceptable salt thereof, is to be administered once daily.

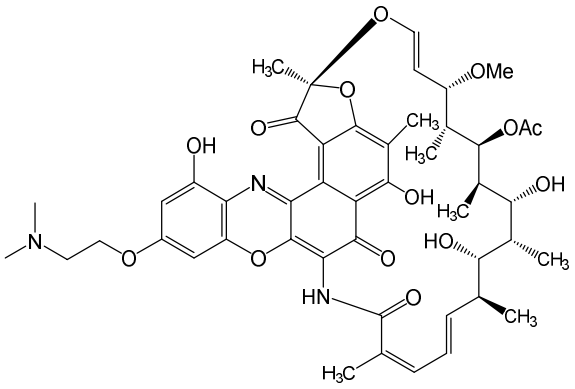
32. The use of any one of claims 9-31, wherein the subject is human.

33. A pharmaceutical composition comprising a) a compound selected from



(I)

and



(II), or a pharmaceutically acceptable salt thereof,

b) vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, and

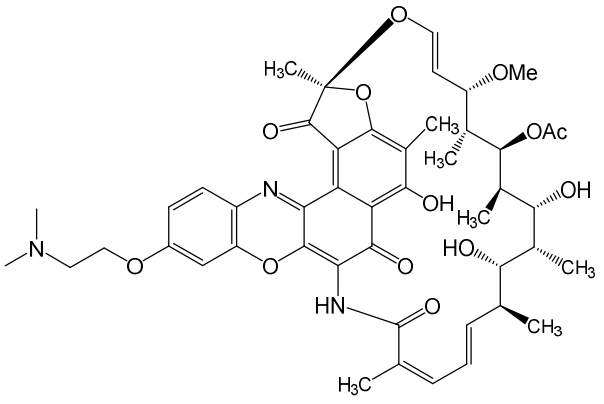
c) a pharmaceutically acceptable carrier.

34. The pharmaceutical composition of claim 33 comprising from about 0.01 mg to about 5000 mg of vancomycin or a derivative thereof.

35. The pharmaceutical composition of claim 33 comprising from about 0.001 mg to about 5000 mg of the compound (I) or (II).

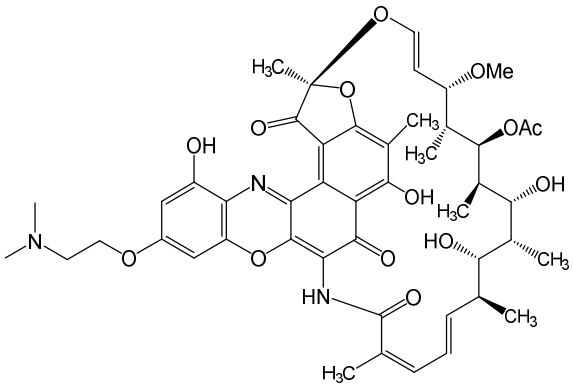
36. The pharmaceutical composition of claim 33 comprising from about 0.01 mg to about 500 mg of the compound (I) or (II).

37. A pharmaceutical dosage form comprising a) a compound selected from



(I)

and



(II), or a pharmaceutically acceptable salt thereof,

b) vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, and

c) a pharmaceutically acceptable vehicle.

38. The pharmaceutical dosage form of claim 37, wherein the dosage form is an oral dosage form or an injectable dosage form.

39. The pharmaceutical dosage form of claim 37 comprising from about 0.01 mg to about 5000 mg of vancomycin or a derivative thereof.

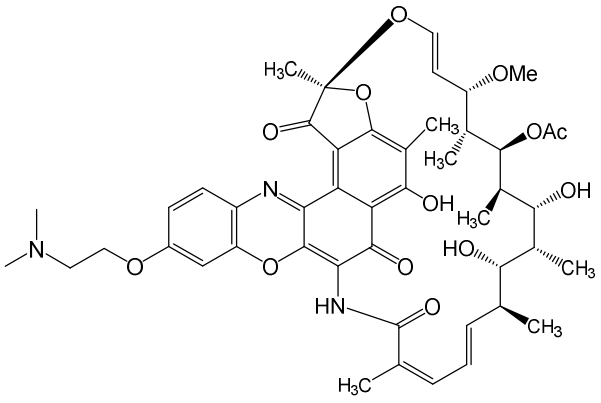
40. The pharmaceutical dosage form of claim 37 comprising from about 0.001 mg to about 5000 mg of the compound (I) or (II).

41. The pharmaceutical dosage form of claim 37 comprising from about 0.01 mg to about 500 mg of the compound (I) or (II).

42. The pharmaceutical dosage form of any of claims 37-41 formulated for a single administration.

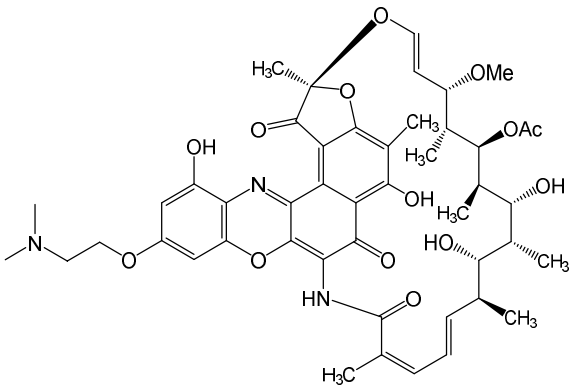
43. The pharmaceutical dosage form of any of claims 37-41 formulated for multiple administrations.

44. A kit comprising a) a first container comprising a compound selected from



(I)

and



(II), or a pharmaceutically acceptable salt thereof,

b) a second container comprising vancomycin or a derivative thereof, or a pharmaceutically acceptable salt thereof, and

c) instructions for administration of the compound (I) or (II) and the vancomycin or a derivative thereof.

45. The kit of claim 44, wherein the first container comprises compound (I) or a pharmaceutically acceptable salt thereof.

46. The kit of claim 44, wherein the first container comprises compound (II) or a pharmaceutically acceptable salt thereof.