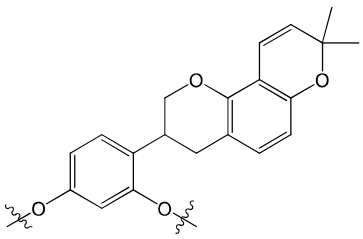
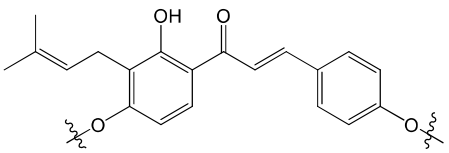
In an aspect, there is provide a compound having the following formula (I):

$$Z^1—L^1—A—L^2—Z^2$$ formula (I)

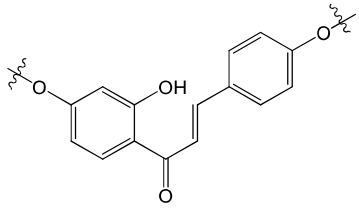
wherein A is a hydrophobic moiety selected from the group consisting of:

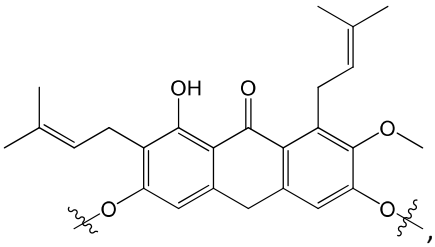


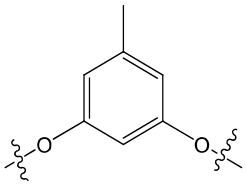
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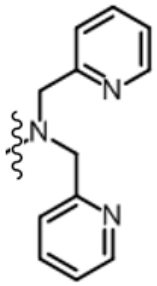
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, and any mixture thereof;

L^1 and L^2 are independently a linker, wherein the linker is independently a C_2 – C_6 alkyl; and

Z^1 and Z^2 independently has the following structure:



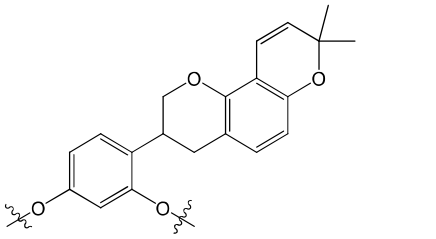
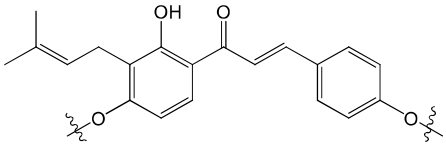
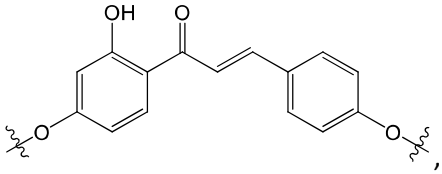
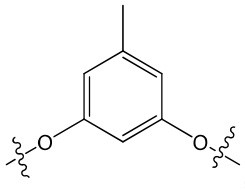
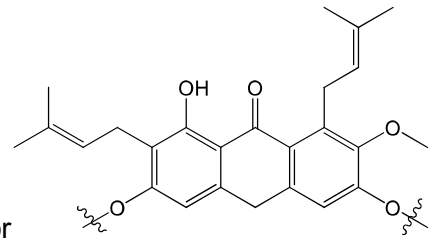
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wherein the broken bond represents where the structure attaches to the remainder of formula (I).

In another aspect, there is provided a compound having the following formula (I):

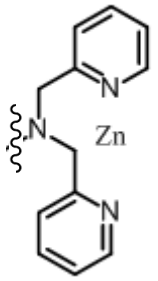
$$Z^1—L^1—A—L^2—Z^2$$ formula (I)

wherein A is a hydrophobic moiety selected from the group consisting of:


,

,

,

, or

;

L^1 and L^2 is independently a linker, wherein the linker is independently a C_2 – C_6 alkyl; and

Z^1 and Z^2 independently has the following structure:


,

wherein the broken bond represents where the structure attaches to the remainder of formula (I).

Advantageously, the compound may have a suitable structure for interacting and disrupting the bacterial membrane. That is, the compound may have two head group regions that interact with the bacterial membrane and a hydrophobic moiety that interacts with the lipid component of the bacterial membrane. The compound may have a suitable size that allows it to span the lipid bilayer of the bacterial membrane. Advantageously, the head groups may comprise a N-atom, having a high pKa value. Further advantageously, the hydrophobic moiety may be large. More advantageously, the hydrophobic moiety may be planar. Taken together, the components of the compound may confer high membrane interaction and antimicrobial properties to the compound.

Advantageously, the N-containing moiety, the guanidine, the zinc chelating complex, all share the same feature of having high affinity with phosphate groups in the bacterial membrane. The strong interactions between the terminal groups (Z^1 or Z^2) of compound of formula (I) and phosphate groups of membrane lead to large membrane perturbations. Advantageously, the N-containing moiety may disrupt the electrostatic interactions (e.g., the

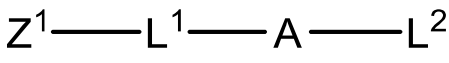
hydrogen bonding network) that stabilize the bacterial membrane. Advantageously, this may result in bacterial cell kill. Alternatively, the disruption of the hydrogen bonding network may facilitate other antibiotics such as colistin to act effectively to result in bacterial cell kill. Colistin may interact with lipid A even when the bacteria is resistant to colistin, and that small perturbance of the outer membrane may allow the compound of formula (I) to enter into the Lipid A structure toward the inner membrane along with colistin, resulting in a fatal disruption of the inner membrane and killing of the bacterium.

The compound of formula (I) may be effective in killing Gram positive bacteria alone or when co-administered with colistin. The compound of formula (I) may be effective in killing Gram negative bacteria that are MCR positive alone or when co-administered with colistin. In such a case, the N-containing moiety may chelate with zinc, which therefore may bind to zinc-dependent MCR and disrupt its activity. The compound of formula (I) may also be effective in killing Gram negative bacteria that are MCR negative yet still resistant to colistin, when co-administered with colistin. In addition, the compound of formula (I) may be effective in killing a wide range of Gram negative bacteria, including bacteria that are resistant to carbapenems, when co-administered with colistin. Thus, the compound of formula (I) may overcome the resistance of the bacteria to colistin, restore the action of colistin and in fact extend the action of colistin to Gram negative bacteria that are resistant to carbapenems or colistin alone. Advantageously, the compound of formula (I) is also effective at killing a large number of bacteria without having to change the drug concentration depending on the bacteria species. The only other known antibiotic that is able to achieve this is alcohol, but alcohol is known to be toxic.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above, or a pharmaceutically acceptable salt or hydrate thereof, in association with a pharmaceutically acceptable carrier.

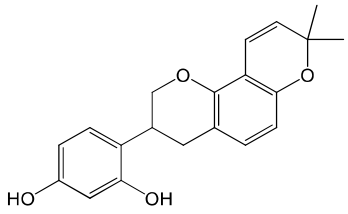
In another example, there is provided a process for preparing a compound as defined above, comprising the step of contacting a hydrophobic moiety with an N-containing moiety under reaction conditions.

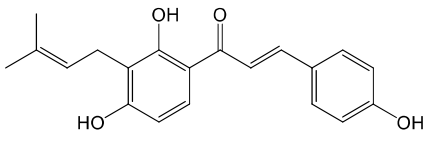
In another aspect, there is provided a process for preparing a compound,wherein the compound has the following formula (I):



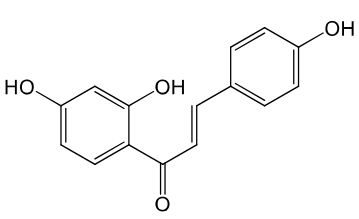
formula (I)

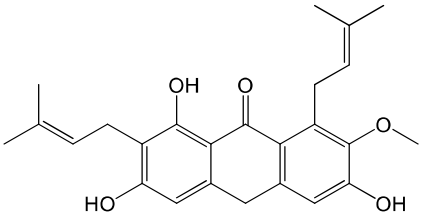
wherein A is a hydrophobic moiety selected from the group consisting of:

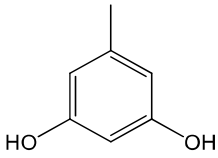


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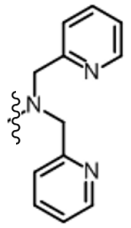


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L^1 and L^2 are independently a linker, wherein the linker is independently a C_2 – C_6 alkyl; and

Z^1 and Z^2 independently has the following structure:



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wherein the broken bond represents where the structure attaches to the remainder of formula (I), and

wherein the process comprises the steps of:

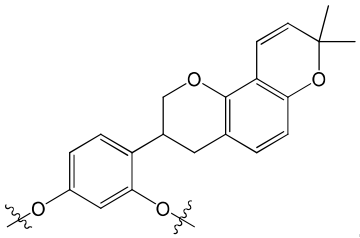
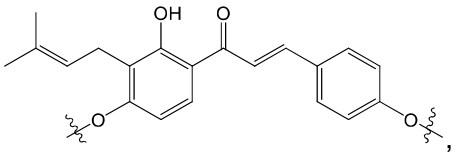
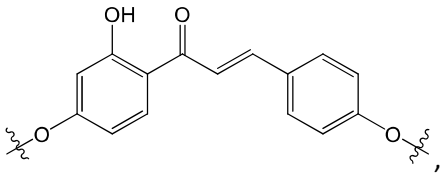
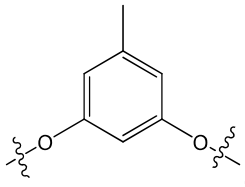
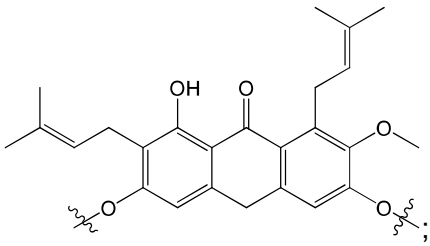
1) contacting a hydrophobic moiety with a linker under reaction conditions; and

2) contacting the linker with a N-containing moiety under reaction condition.

A process for preparing a compound, wherein the compound has the following formula (I):

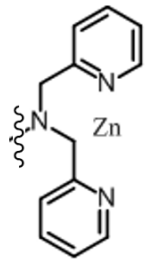
$$Z^1——L^1——A——L^2——Z^2$$ formula (I)

wherein A is a hydrophobic moiety selected from the group consisting of :


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,

,

, or

;

L^1 and L^2 are independently a linker, wherein the linker is independently a $C_2 – C_6$ alkyl; and

Z^1 and Z^2 independently has the following structure:


,

wherein the broken bond represents where the structure attaches to the remainder of formula (I), and

wherein the process comprises the steps of:

1) contacting a hydrophobic moiety with a linker under reaction conditions;
2) contacting the linker with a N-containing moiety under reaction conditions; and
3) adding zinc after the N-containing moiety is covalently bonded to the linker.

Advantageously, the process for preparing the compound is facile, using mild reaction conditions, facilitating low cost and large scale synthesis of the compounds.

In another example, there is provided the use of the compound as defined above or the pharmaceutical composition as defined above, as an antibiotic.

In another example, there is provided the use of the compound as defined above or the pharmaceutical composition as defined above, to kill or inhibit the growth of a microorganism in vitro.

In another aspect, there is provided the use of the compound as defined above or the pharmaceutical composition as defined above, to kill a bacterium in vitro, wherein the compound as defined above or the pharmaceutical composition as defined above is used in conjunction with colistin.

In another aspect, there is provided a compound as defined above for use in therapy.

In an example, there is provided a method for treating a bacterial infection, the method comprising the step of administering to a patient in need thereof a therapeutically effective amount of a compound as defined above.

In another example, there is provided a compound as defined above for use in treating a bacterial infection.

In another example, there is provided the use of a compound as defined above in the manufacture of a medicament for the treatment of a bacterial infection.

In another aspect, there is provided the use of a compound as defined above in the manufacture of a medicament for the treatment of a bacterial infection, wherein the compound as defined above is to be administered in conjunction with colistin.

Advantageously, the compound may act either as an antibiotic in its own right or as an adjuvant to other antibiotics such as colistin, by facilitating disruption of the outer membrane of MCR mutated bacteria as well as other Gram negative bacteria without MCR mutation, and to restore the sensitivity of these strains to colistin. Advantageously, the compound may reduce the MIC of colistin by at least twice.

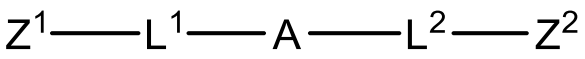
DEFINITIONS

"Alkyl" as a group or part of a group refers to a straight or branched aliphatic hydrocarbon group, preferably a C_1–C_{20} alkyl, C_1–C_{12} alkyl, more preferably a C_1-C_{10} alkyl, most preferably C_1-C_6 unless otherwise noted. Examples of suitable straight and branched C_1-C_6 alkyl substituents include methyl, ethyl, n-propyl, 2-propyl, n-butyl, sec-butyl, t-butyl, hexyl, and the like. The group may be a terminal group or a bridging group.

"Alkenyl" as a group or part of a group denotes an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched preferably having 2-20 carbon atoms, preferably having 2-12 carbon atoms, more preferably 2-10 carbon atoms, most preferably 2-6 carbon atoms, in the normal chain. The group may contain a plurality of double bonds in the normal chain and the orientation about each is independently E or Z. Exemplary alkenyl groups include, but are not limited to, ethenyl,

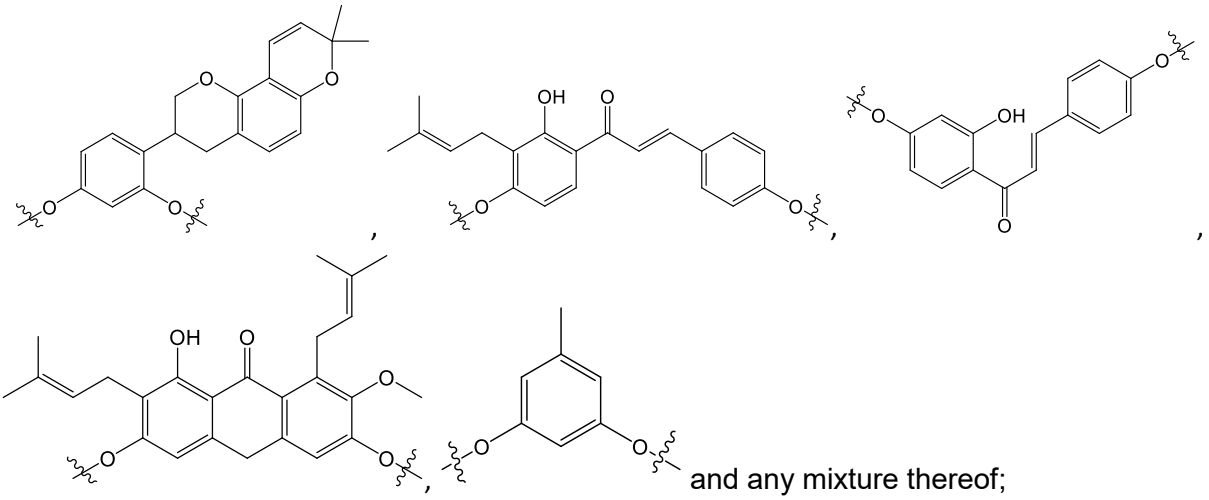
Claims

1. A compound having the following formula (I):



formula (I)

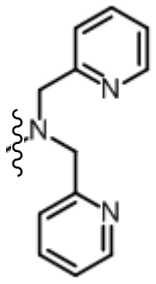
wherein A is a hydrophobic moiety selected from the group consisting of:



and any mixture thereof;

L^1 and L^2 are independently a linker, wherein the linker is independently a C_2 – C_6 alkyl; and

Z^1 and Z^2 independently has the following structure:

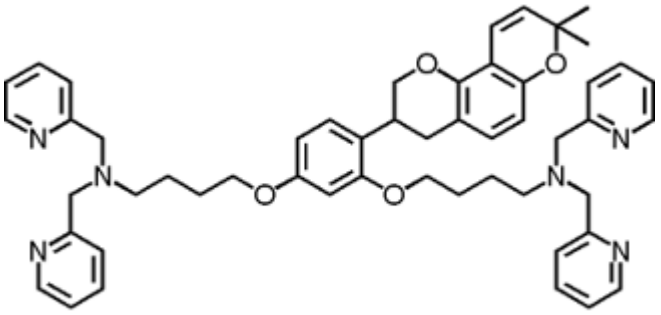


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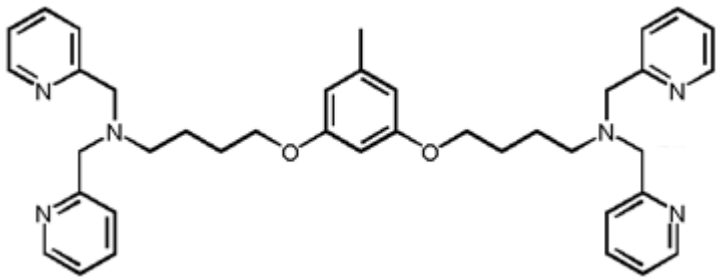
wherein the broken bond represents where the structure attaches to the remainder of formula (I).

2. The compound according to claim 1, wherein the compound of formula (I) has a logP value greater than 4.

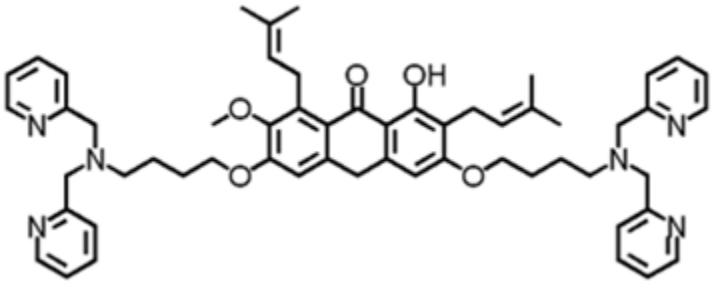
3. The compound according to claim 1 or 2, wherein the compound of formula (I) has the following structure:



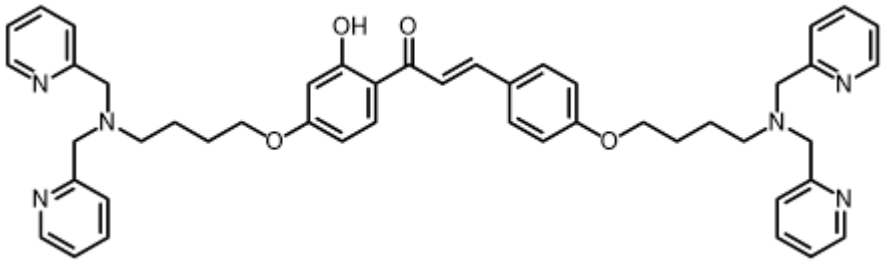
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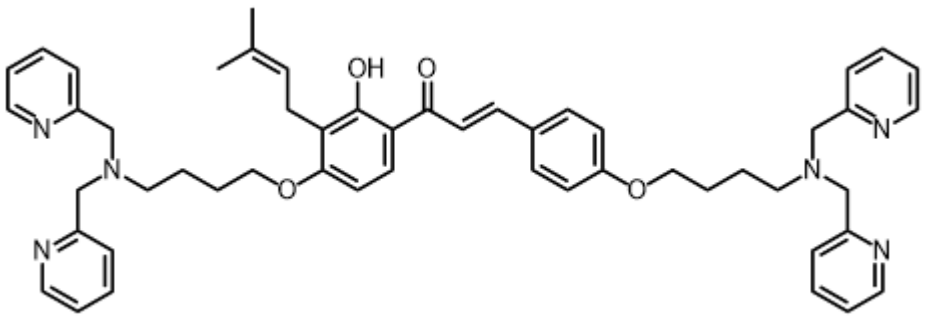
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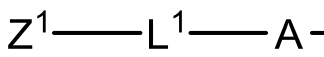


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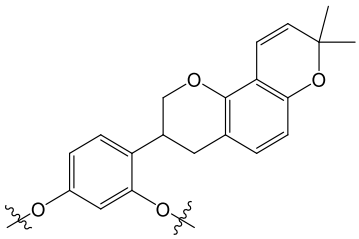
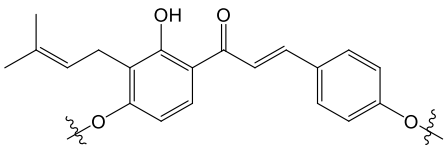
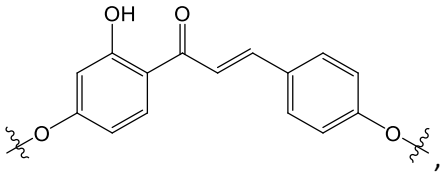
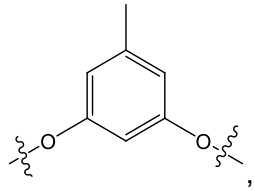
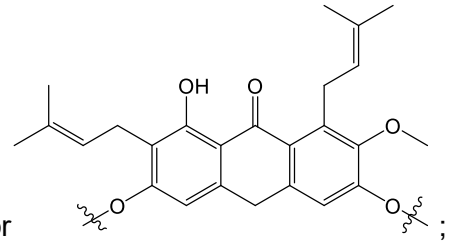
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4. A compound having the following formula (I):



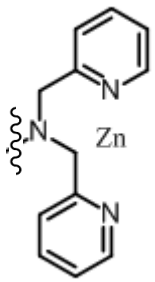
formula (I)

wherein A is a hydrophobic moiety selected from the group consisting of:


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, or

;

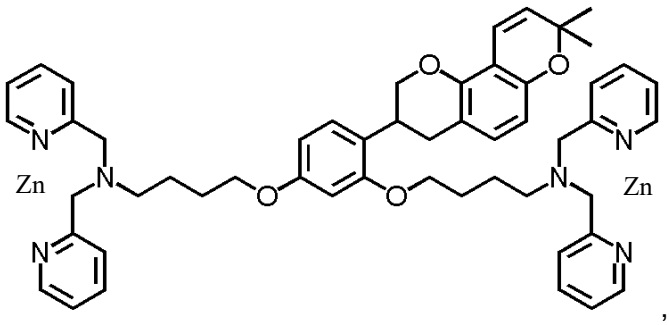
L^1 and L^2 is independently a linker, wherein the linker is independently a C_2 – C_6 alkyl; and

Z^1 and Z^2 independently has the following structure:

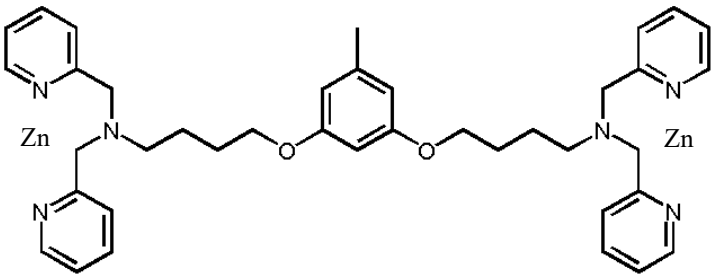

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wherein the broken bond represents where the structure attaches to the remainder of formula (I).

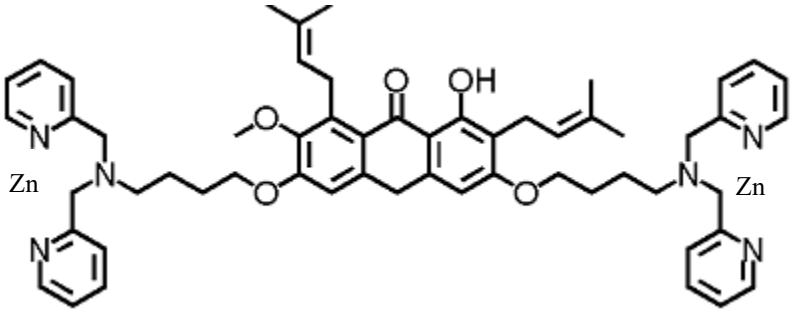
5. The compound of according to claim 4, wherein the compound of formula (I) has the following structure:



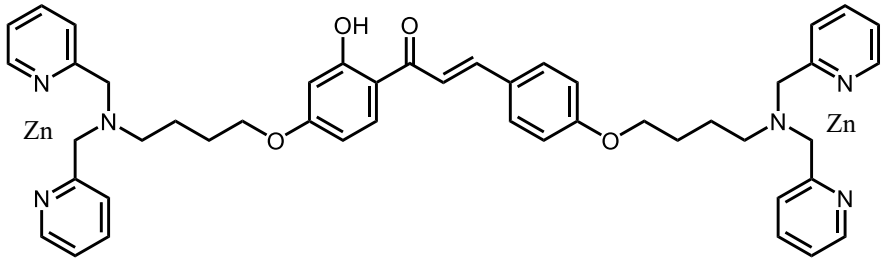
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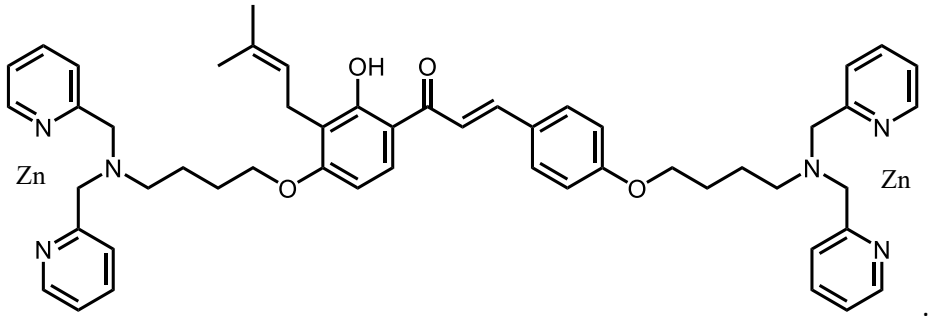
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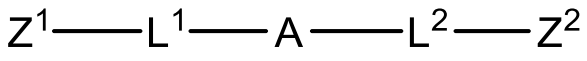


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6. A pharmaceutical composition comprising a compound according to claim 4 or 5, or a pharmaceutically acceptable salt or hydrate thereof, in association with a pharmaceutically acceptable carrier.

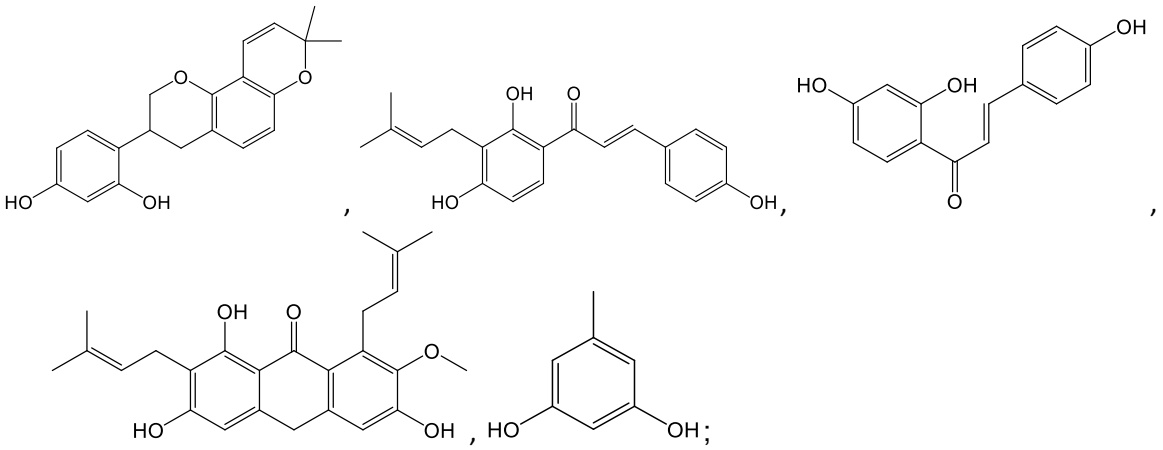
7. The pharmaceutically composition according to claim 6, wherein the pharmaceutically acceptable carrier is saline.

8. A process for preparing a compound, wherein the compound has the following formula (I):



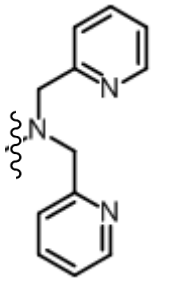
formula (I)

wherein A is a hydrophobic moiety selected from the group consisting of:



L^1 and L^2 are independently a linker, wherein the linker is independently a $C_2 – C_6$ alkyl; and

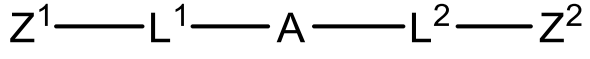
Z^1 and Z^2 independently has the following structure:



wherein the broken bond represents where the structure attaches to the remainder of formula (I), and

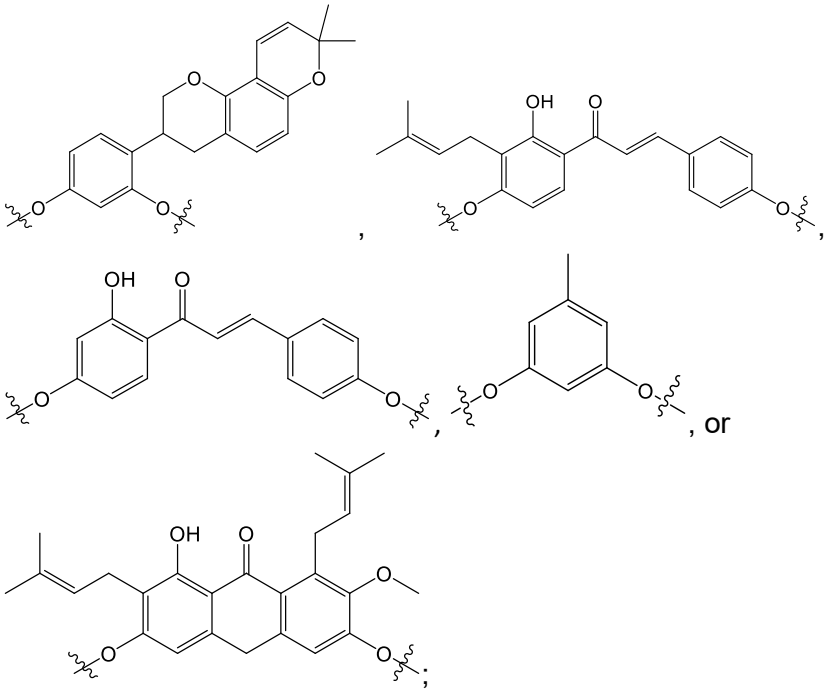
wherein the process comprises the steps of:
1) contacting a hydrophobic moiety with a linker under reaction conditions; and
2) contacting the linker with a N-containing moiety under reaction conditions.

9. A process for preparing a compound, wherein the compound has the following formula (I):



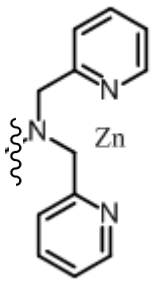
formula (I)

wherein A is a hydrophobic moiety selected from the group consisting of :



L^1 and L^2 are independently a linker, wherein the linker is independently a $C_2 – C_6$ alkyl; and

Z^1 and Z^2 independently has the following structure:



,

wherein the broken bond represents where the structure attaches to the remainder of formula (I), and

wherein the process comprises the steps of:
1) contacting a hydrophobic moiety with a linker under reaction conditions;
2) contacting the linker with a N-containing moiety under reaction conditions; and
3) adding zinc after the N-containing moiety is covalently bonded to the linker.

10. The process according to claim 8 or 9, wherein a covalent bond is formed between the hydrophobic moiety and the linker or between the linker and the N-containing moiety.

11. The process according to any one of claims 8 to 10, wherein the linker is selected from the group consisting of 1,4-dibromobutane, 1,3-diiodobutane, 1,2-dibromoethane, 1,3-dibromopropane, 1,4-diiodobutane and any combination thereof.

12. The process according to any one of claims 8 to 11, wherein the contacting is done in a solvent selected from the group consisting of acetone, methanol, ethanol, propanol, butanol, N,N-dimethylformamide, dimethylsulfoxide, tetrahydrofuran, dichloromethane, pyridine, water and any mixture thereof.

13. The process according to any one of claims 8 to 12, wherein the contacting step is performed at a temperature in the range of 21 °C to 160 °C.

14. The process according to any one of claims 8 to 13, wherein the contacting step is performed for a duration in the range of 2 hours to 36 hours.

15. Use of the compound according to claim 4 or 5 or the pharmaceutical composition according to claim 6, to kill a bacetrium in vitro, wherein the compound according to claim 4 or 5 or the pharmaceutical composition according to claim 6 is used in conjunction with colistin.

16. The use according to claim 15, wherein the bacterium is a Gram negative or Gram positive bacterium.

17. The use according to claim 15 or 16, wherein the bacterium is MCR positive or MCR negative.

18. The use according to any one of claims 15 to 17, wherein the bacterium is carbapenem-resistant.

19. A compound according to claim 4 or 5 for use in therapy.

20. Use of a compound according to claim 4 or 5 in the manufacture of a medicament for the treatment of a bacterial infection, wherein the compound according to claim 4 or 5 is to be administered in conjunction with colistin.

21. The use according to claim 20, wherein the compound according to claim 4 or 5 is present at an amount in the range of 2 μg/mL to 75 μg/mL.

22. The use according to claim 20 or 21, wherein the compound according to claim 4 or 5 and colistin are present at an equal amount by weight, or the compound according to claim 4 or 5 is present in excess of 1.5 to 6 times of colistin by weight.

23. The use according to any one of claims 20 to 22, wherein colistin is present at a range of 1 mg/kg to 10 mg/kg and the compound according to claim 4 or 5 is present at a range of 10 mg/kg to 50 mg/kg.

24. The use according to any one of claims 20 to 23, wherein the compound according to claim 4 or 5 is to be administered intramuscularly, intraperitoneally, topically, subcutaneously or intravenously.