In another aspect, 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.

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

In another aspect, 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 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 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.

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.

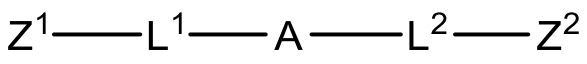
DEFINITIONS

"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;

L^1 and L^2 are independently a linker; and

Z^1 and Z^2 are independently an N-containing moiety.

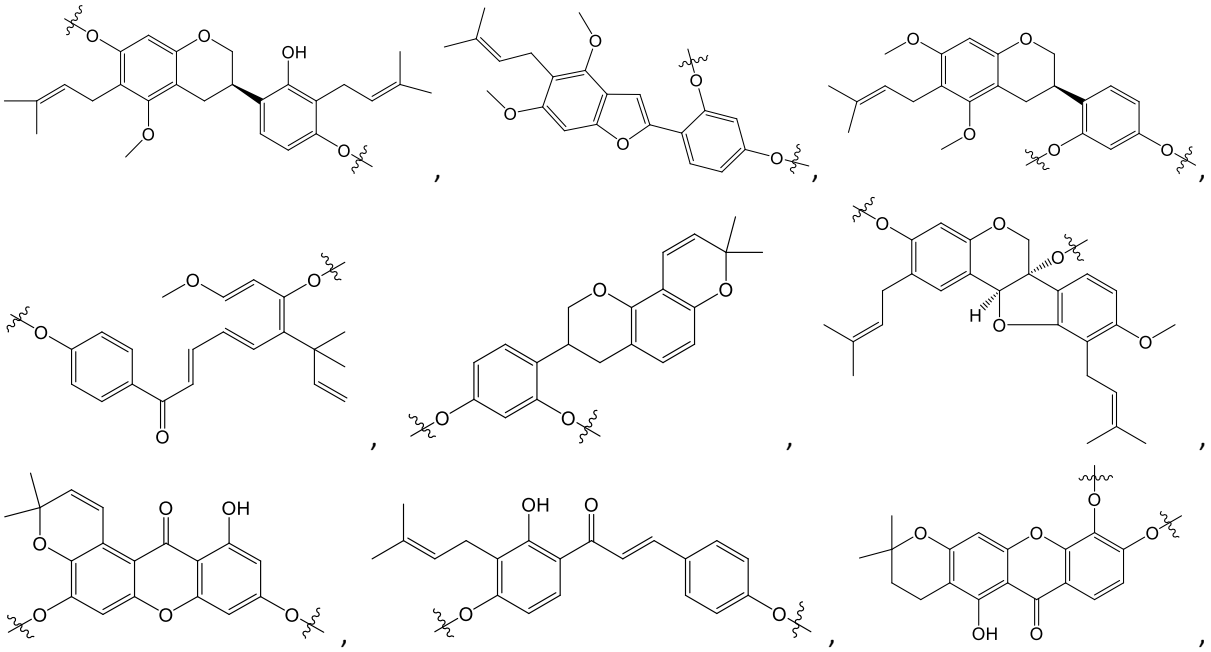
2. The compound according to claim 1, wherein A comprises at least one substituted or unsubstituted aryl.

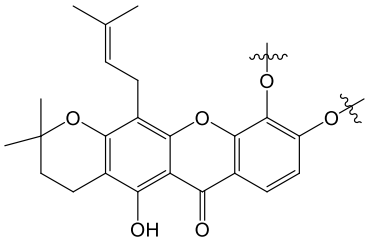
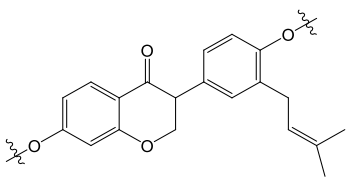
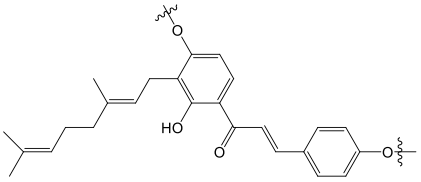
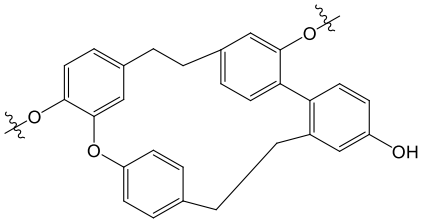
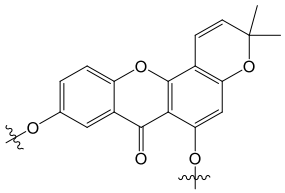
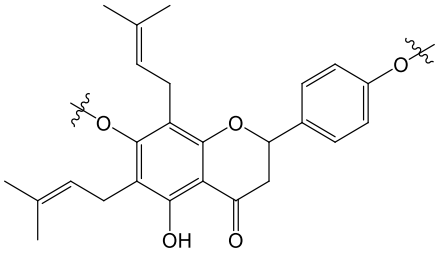
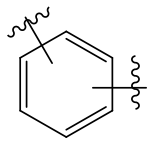
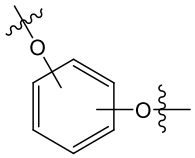
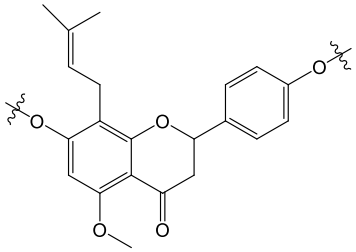
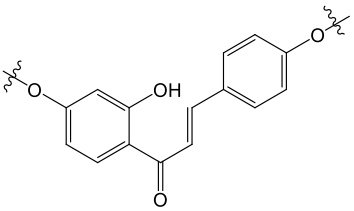
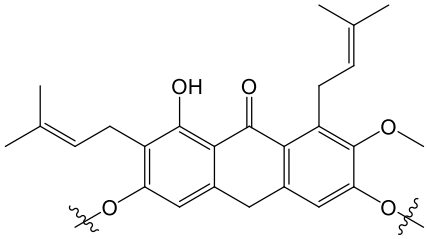
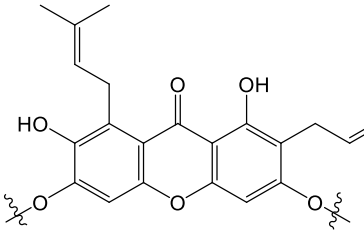
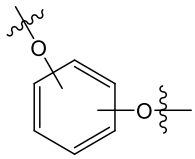
3. The compound according to claim 2, wherein A further comprises at least one alkenyl group.

4. The compound according to claim 3, wherein A is planar or substantially planar.

5. The compound according to claim 4, wherein A further comprises at least one isoprenyl group.

6. The compound according to any one of the preceding claims, wherein A is selected from the group consisting of:

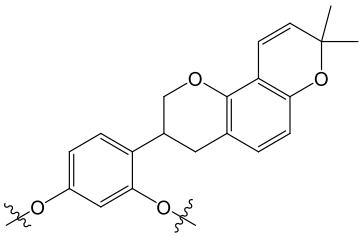
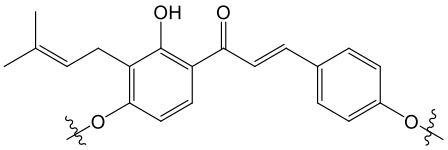
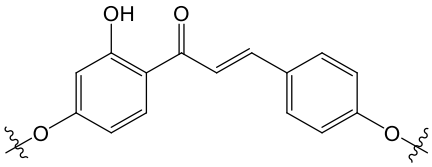
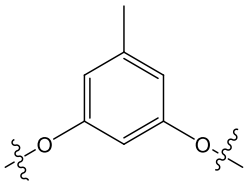
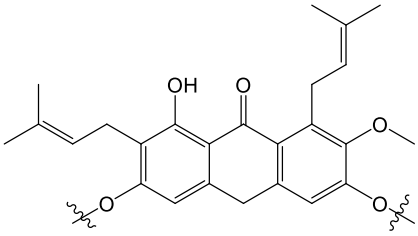
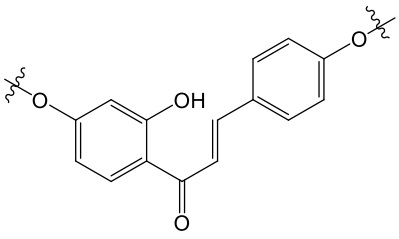


, and any mixture thereof,

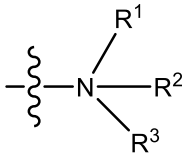
wherein the broken bond represents where the structure attaches to the remainder of formula (I).

7. The compound according to claim 6, wherein A is selected from the group consisting of:


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and any mixture thereof.

8. The compound according to any one of the preceding claims, wherein Z^1 and Z^2 independently have a pKa value greater than 9.

9. The compound according to any one of the preceding claims, wherein Z^1 and Z^2 independently have the following structure:



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

R^1 and R^2 are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aminoalkyl, guanidine, substituted or unsubstituted guanidylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, amino acid or peptide, or R^1 and R^2 are taken together to form a saturated or unsaturated, substituted or unsubstituted heterocyclic ring; and

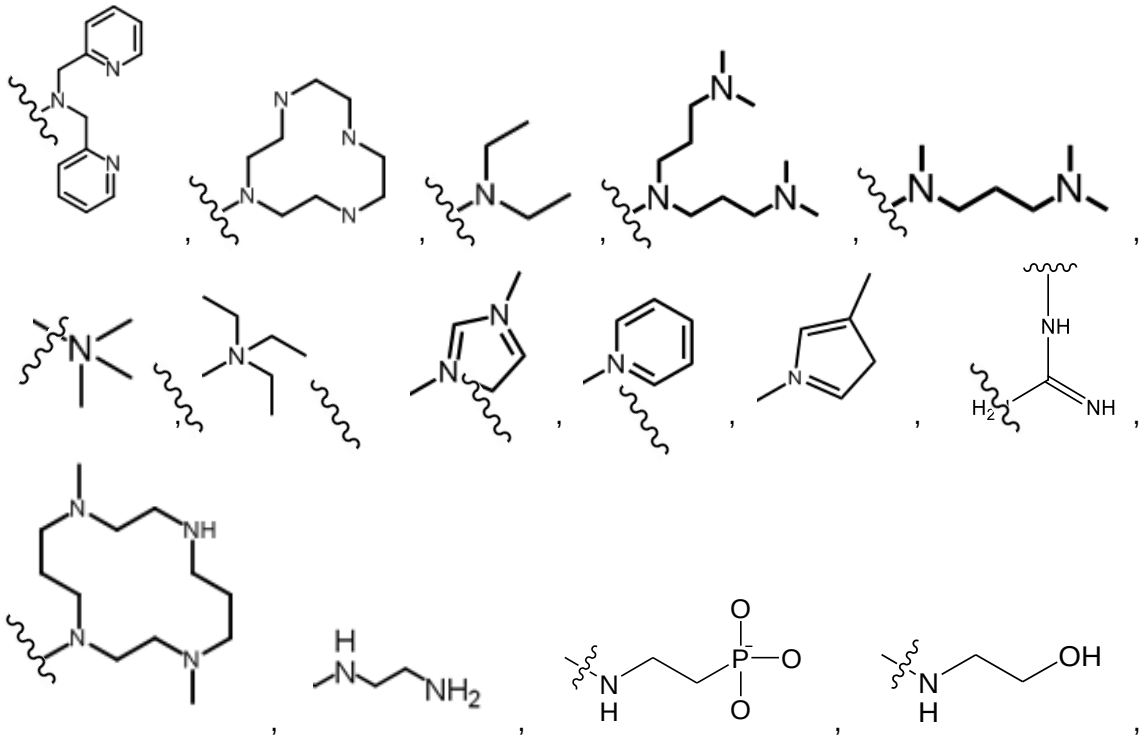
R^3 is absent or hydrogen, or substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aminoalkyl, guanidine, substituted or unsubstituted guanidylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkyl, amino acid or peptide,

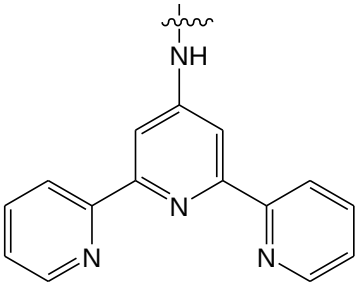
wherein when R^3 is present, the nitrogen atom is a cationic quaternary nitrogen.

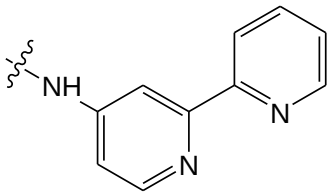
10. The compound according to claim 9, wherein R^1, R^2 and R^3 independently comprise a functional group selected from the group consisting of amine, guanidine, pyrrolidine, pyrrole, imidazolidine, pyrazolidine, imidazole, pyrazole, triazole, piperidine, pyridine, piperazine, diazine, hydroxamic acid, hydrazine, N-hydroxyurea, squaric acid, carbamolyphosphonate, oxazoline, pyrimidinetrione, 1-hydroxy-2(1H)-pyridinone (1,2-HOPO) and any combination thereof.

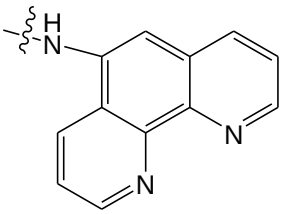
11. The compound according to claim 9 or 10, wherein R^1, R^2 and R^3 are independently selected from the group consisting of methyl, ethyl, propyl, butyl, $-(CH_2)_xNR'R''$, $-(CH_2)_xOH$, $-(CH_2)_xPO_3$, $-(CH_2)_xCR'R''R'''$, $-(C(NH_2)NHC(NH_2))x-NH_2$, guanidine, 2-methylpyridine, 1-methylimidazole, pyridine, bipyridine, terpyridine, phenanthroline, 3-methylpyrrole, cyclen (1,4,7,10-tetraazacyclododecane), cyclam (1,4,8,11-tetraazacyclotetradecane), 1,8-dimethyl-1,4,8,11-tetraazacyclotetradecane, 1,4,7-triazacyclononane, arginine, polyarginine, lysine, polylysine, poly-epsilon lysine and any mixture thereof, wherein x is any integer from 1 to 10, and R', R'' and R''' are independently hydrogen or substituted or unsubstituted alkyl.

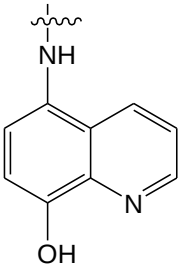
12. The compound according to any one of claims 9 to 11, wherein Z^1 and Z^2 are independently selected from the group consisting of:

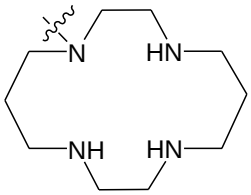


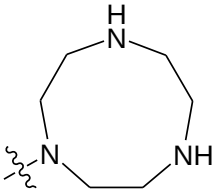


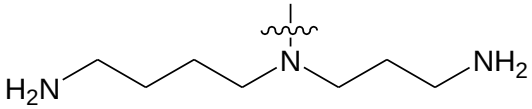
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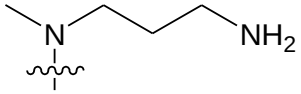
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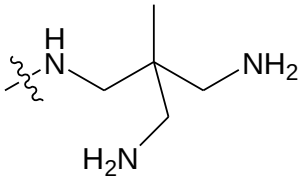
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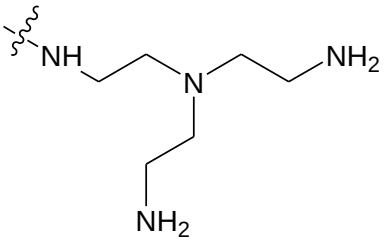
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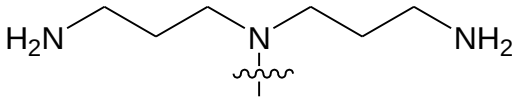
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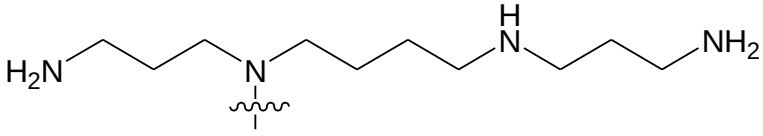
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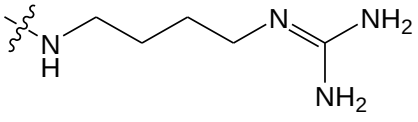
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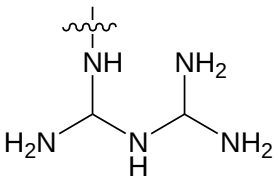
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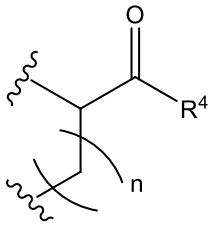
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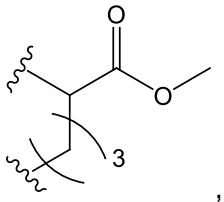
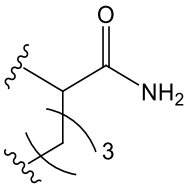
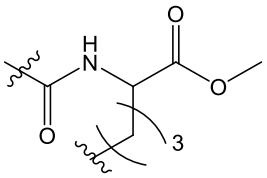
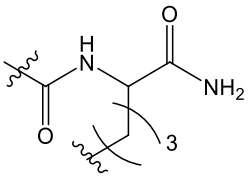
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and any combination thereof.

13. The compound according to any one of the preceding claims, wherein L^1 and L^2 are independently a substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, ester, amide, ether, $-(O-CH_2-CH_2-O)_n-$, L^3 or any combination thereof, wherein L^3 has the following structure:

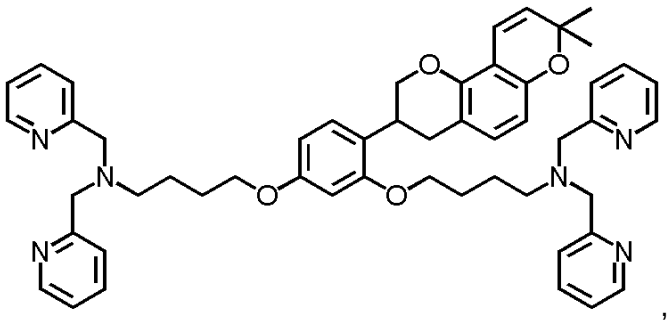


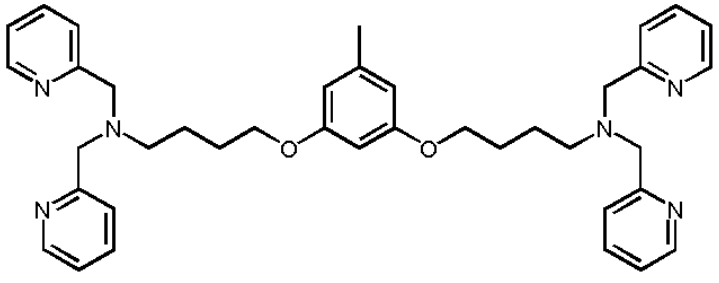
wherein n is an integer from 1 to 10 and R^4 is an amino or a heteroalkyl and the broken bond represents where the structure attaches to the remainder of formula (I).

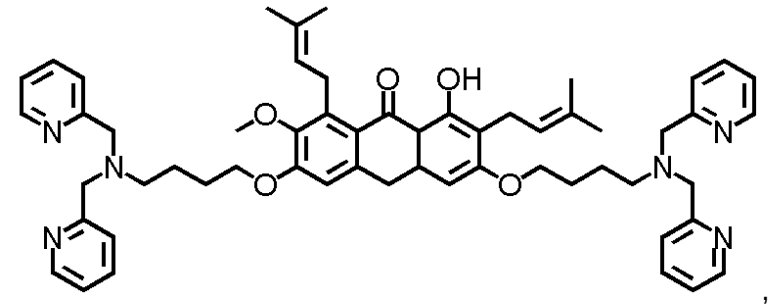
14. The compound according to claim 13, wherein L^1 and L^2 are independently selected from the group consisting of $-(CH_2)_4-$, amide, , , and any combination thereof, or  and .

15. The compound according to any one of the preceding claims, wherein the compound of formula (I) has a logP value greater than 4.

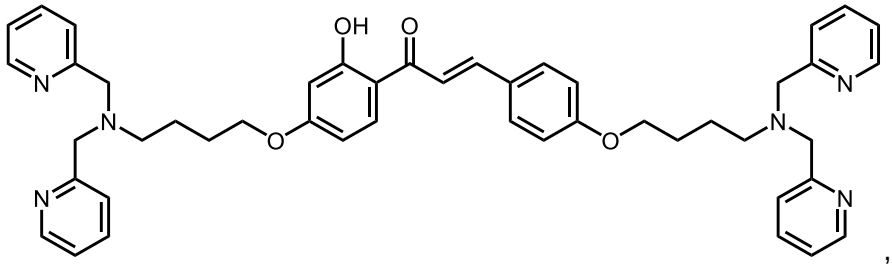
16. The compound according to any one of the preceding claims, wherein the compound of formula (I) has the following structure:

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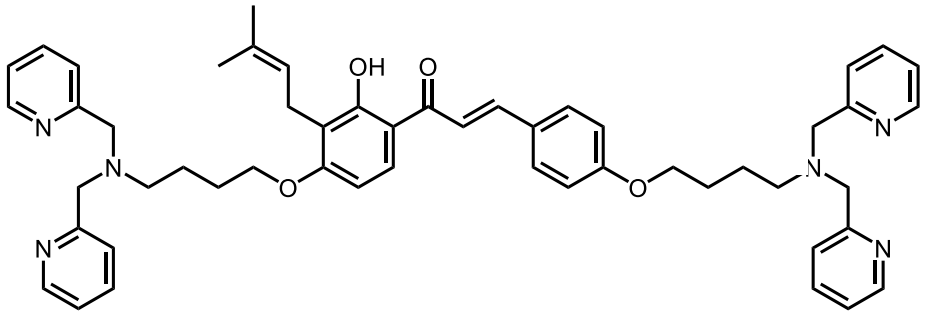
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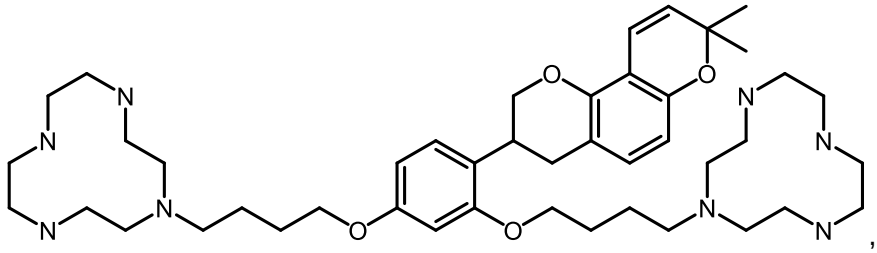


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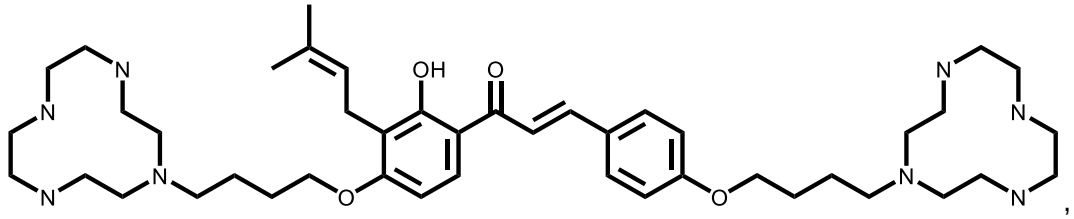


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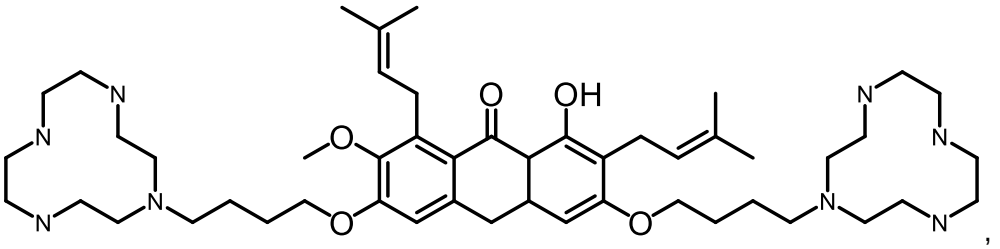


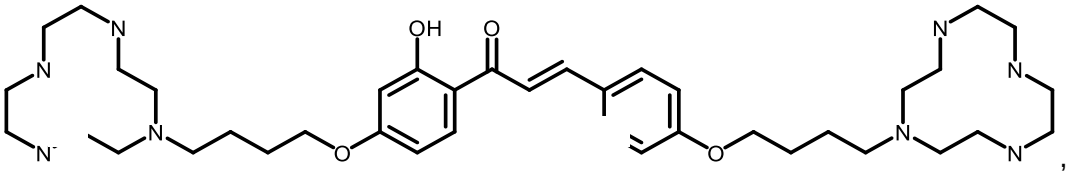


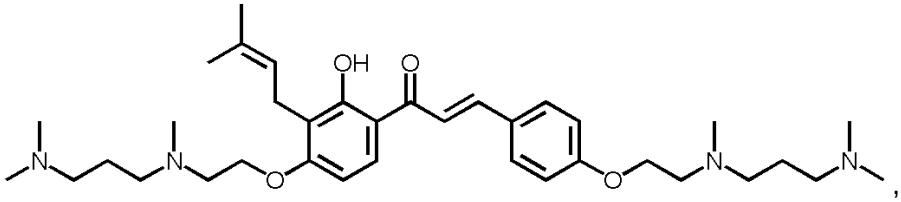
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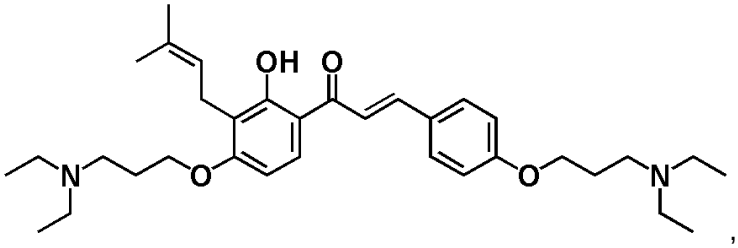


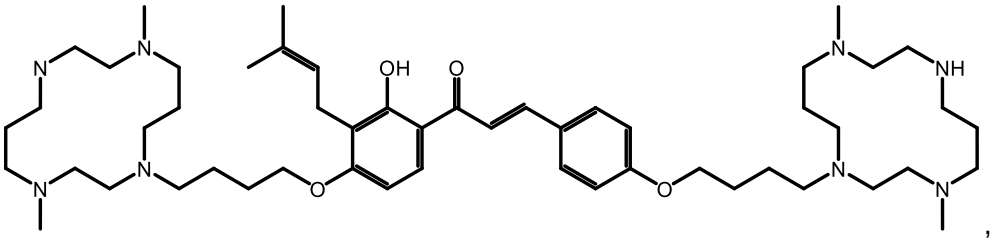
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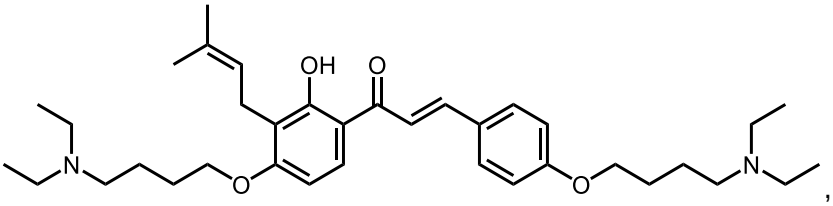


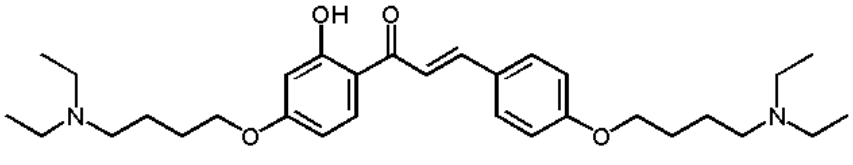


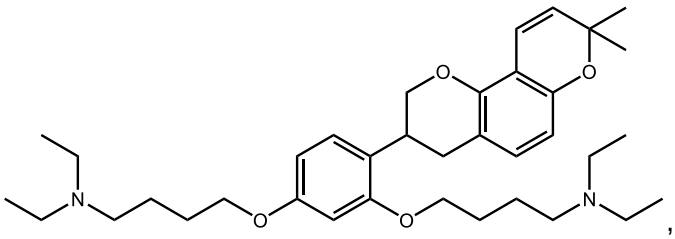


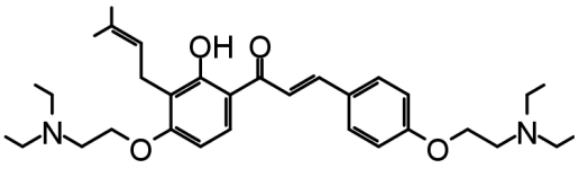


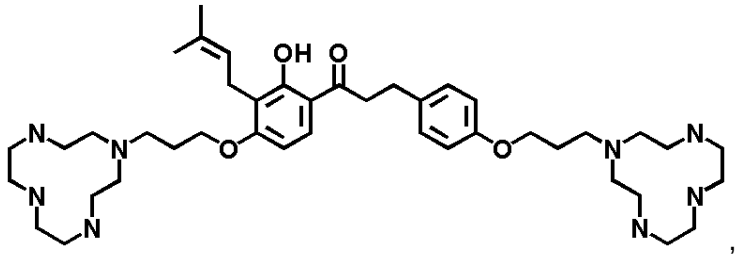


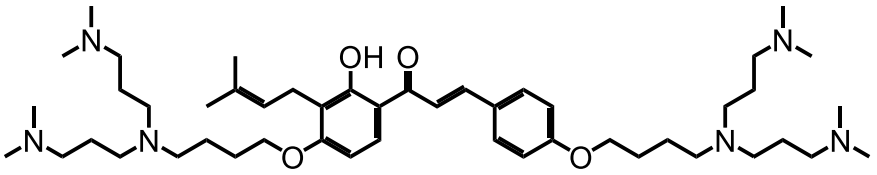


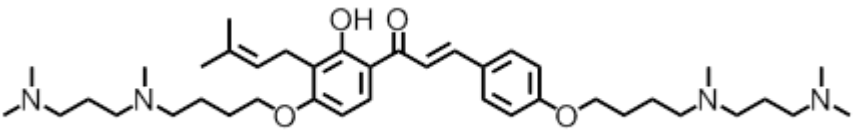


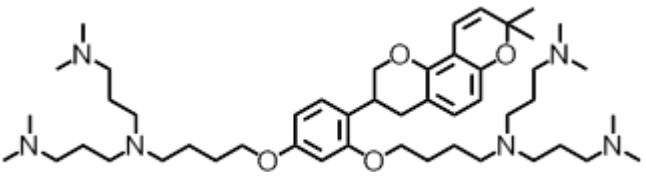


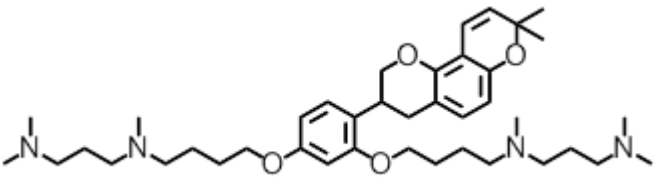


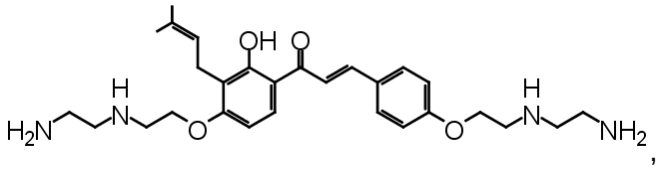


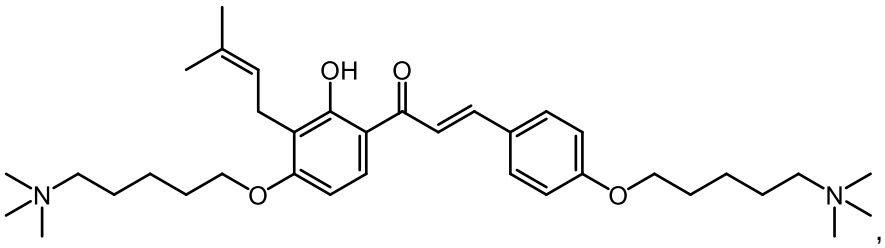


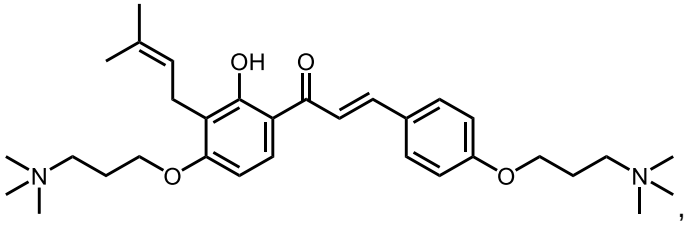


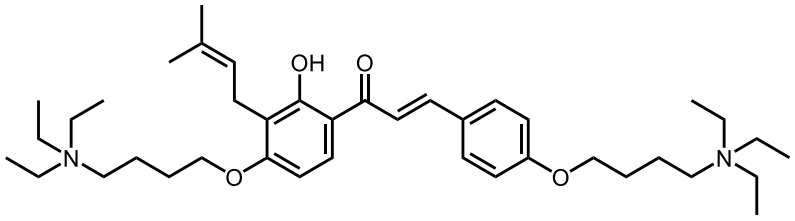


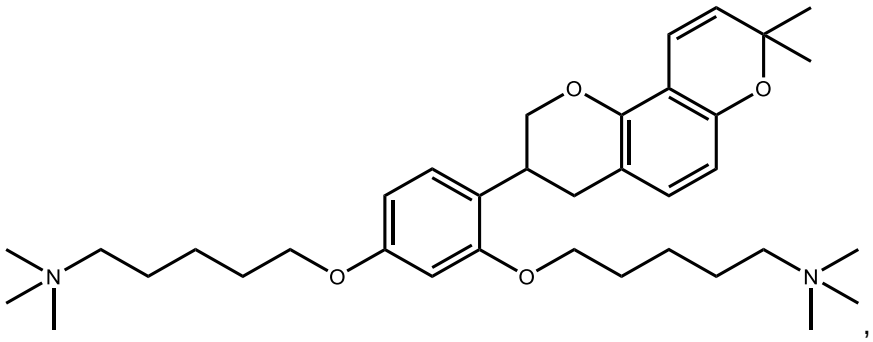


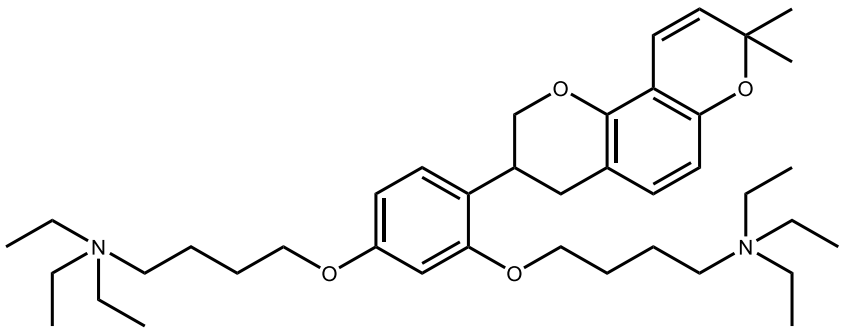


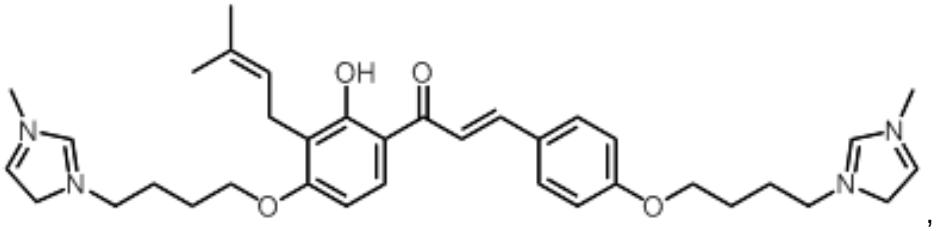


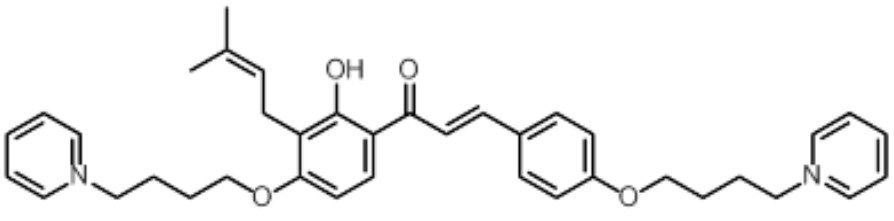


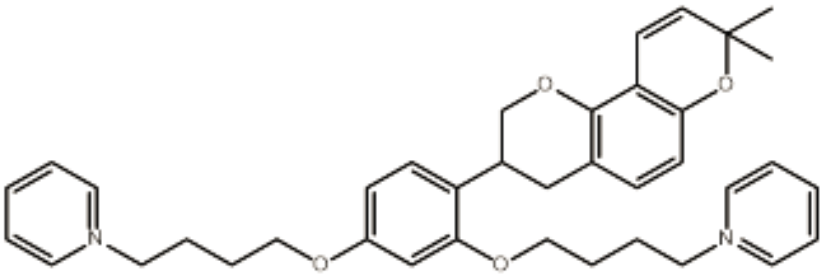


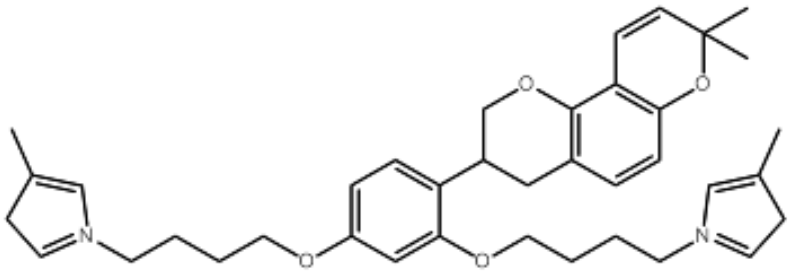


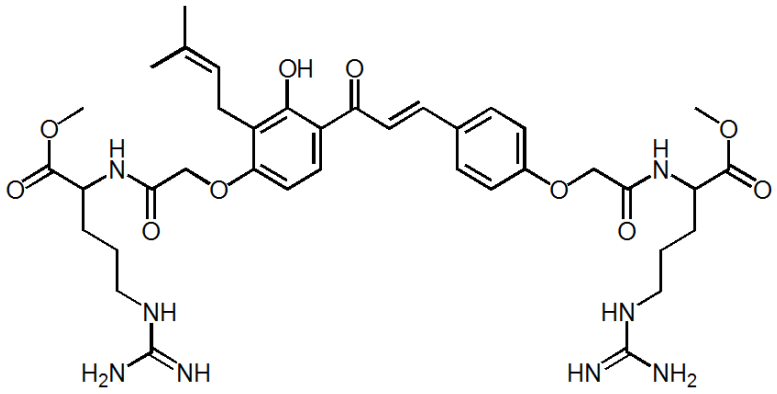


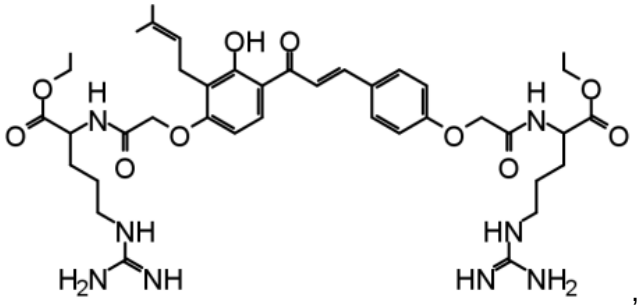

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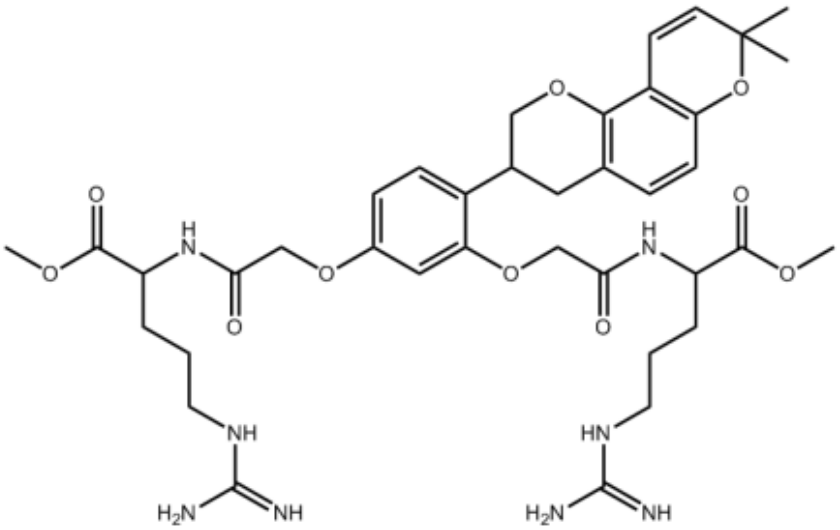

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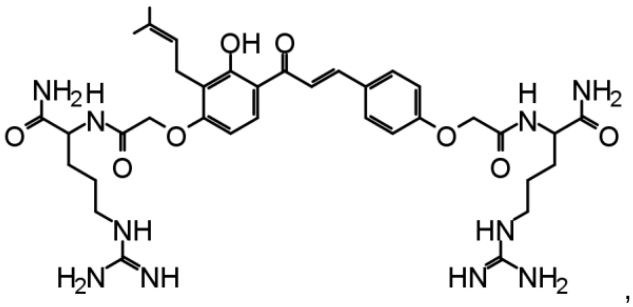

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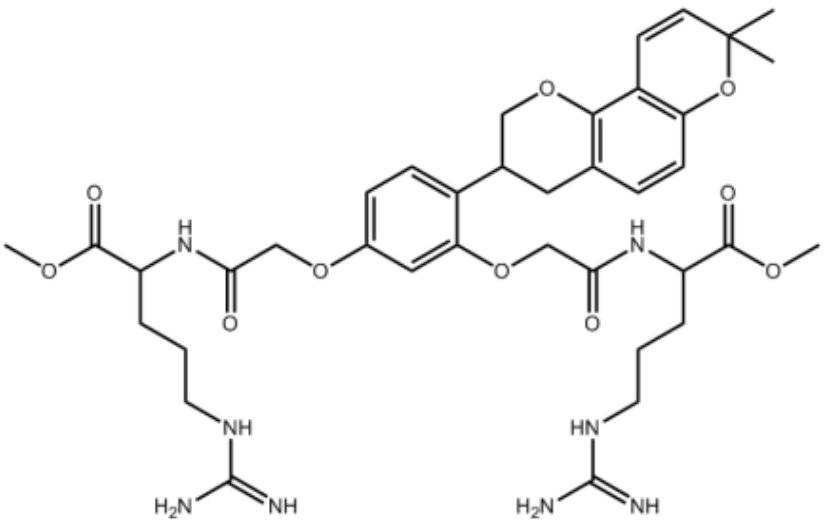
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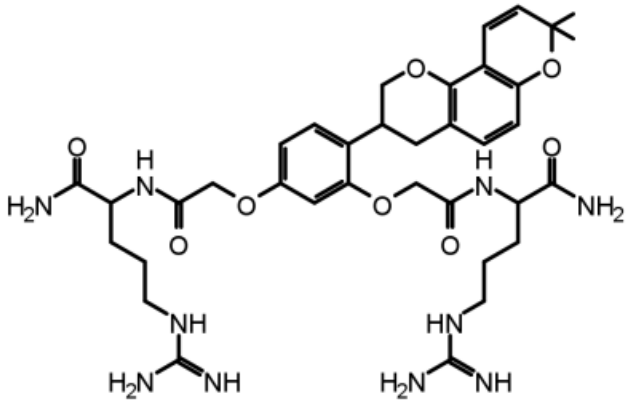
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or



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17. The compound according to any one of the preceding claims, wherein each N-containing moiety is independently chelated to zinc.

18. The compound according to any one of the preceding claims, wherein each N-containing moiety independently has a positive charge.

19. A pharmaceutical composition comprising a compound according to any one of the preceding claims, or a pharmaceutically acceptable salt or hydrate thereof, in association with a pharmaceutically acceptable carrier.

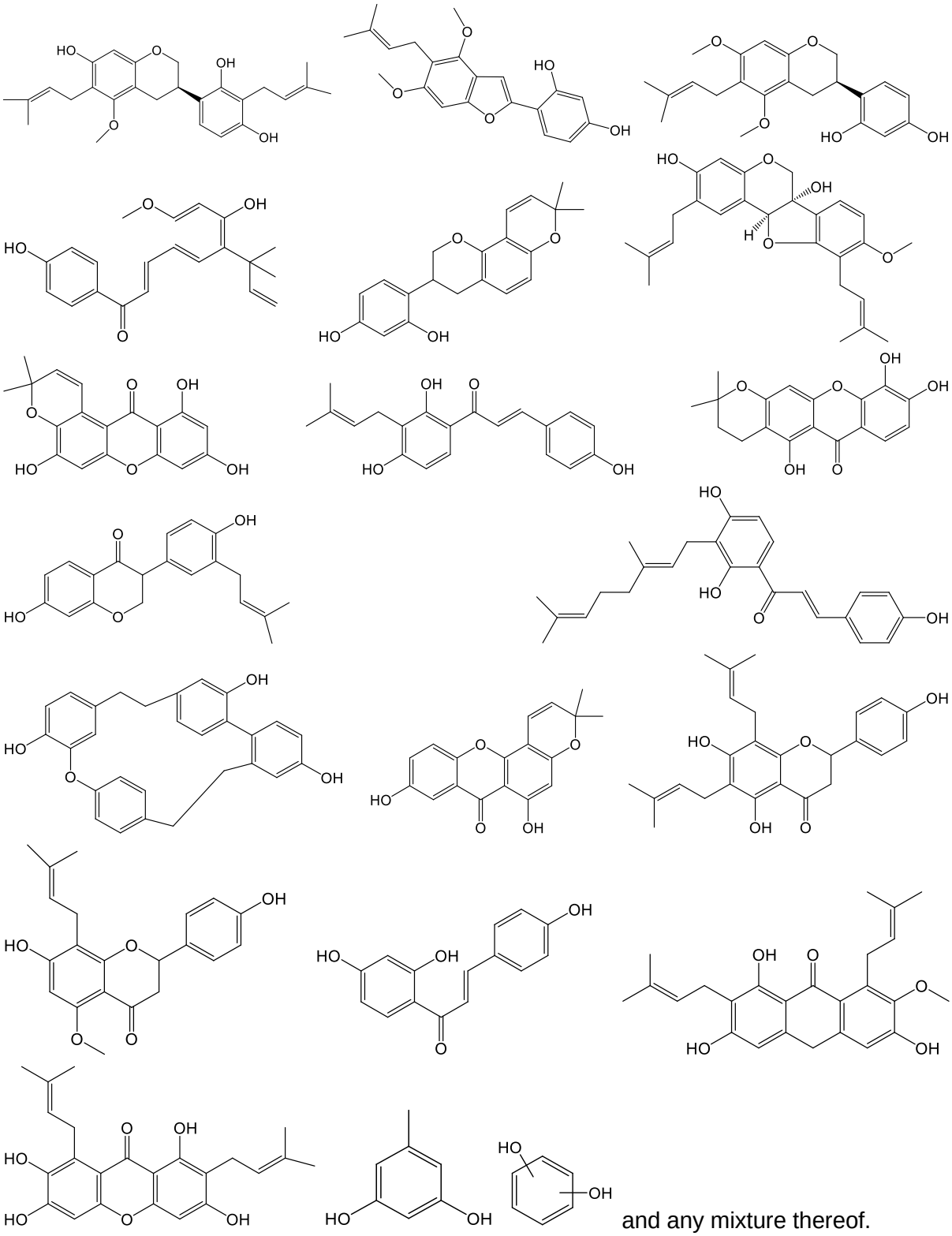
20. The pharmaceutically composition according to claim 19, wherein the pharmaceutically acceptable carrier is saline.

21. A process for preparing a compound according to any one of claims 1 to 18, comprising the step of contacting a hydrophobic moiety with an N-containing moiety under reaction conditions.

22. The process according to claim 21, further comprising the step of contacting the hydrophobic moiety with a linker before contacting with the N-containing moiety.

23. The process according to claim 21 or 22, wherein a covalent bond is formed between the hydrophobic moiety and the N-containing moiety or the hydrophobic moiety and the linker or the linker and the N-containing moiety.

24. The process according to any one of claims 21 to 23, wherein the hydrophobic moiety is selected from the group consisting of:



and any mixture thereof.

25. The process according to any one of claims 21 to 24, wherein the linker is selected from the group consisting of 1,4-dibromobutane, 1,3-diiodobutane, ethyl iodoacetate, hydroxybenzotriazole, 1,2-dibromoethane, 1,3-dibromopropane, methyl iodoacetate, methyl bromoacetate, 1,4-diiodobutane and any combination thereof.

26. The process according to any one of claims 21 to 25, wherein the N-containing moiety is selected from the group consisting of dipicolylamine, cyclen, 1,8-dimethyl,1,4,8,11-tetracyclotetradecane, diethylamine, $-NH[(CH_2)_3N(CH_3)]_2$, $-NH_2(CH_2)_3N(CH_3)_2$, 5-bromopentyltrimethylammonium bromide, 3-bromopentyl trimethylammonium bromide, 4-bromobutyl triethylammonium bromide, 3-(4-Bromobutyl)-1-methylimidazole bromide, 1-(4-Bromobutyl)pyridine bromide, 1-(4-Bromobutyl)pyridine bromide and any combination thereof.

27. The process according to any one of claims 21 to 26, comprising the step of adding zinc after the N-containing moiety is covalently bonded to the linker or hydrophobic moiety.

28. The process according to any one of claims 21 to 27, 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.

29. The process according to any one of claims 21 to 28, wherein the contacting step is performed at a temperature in the range of about 21 °C to about 160 °C.

30. The process according to any one of claims 21 to 29, wherein the contacting step is performed for a duration in the range of about 2 hours to about 36 hours.

31. Use of the compound according to any one of claims 1 to 16 or the pharmaceutical composition according to claim 19 or 20, to kill or inhibit the growth of a microorganism in vitro.

32. The use according to claim 31, wherein the microorganism is a bacterium, archaea, fungus, protist, or any mixture thereof.

33. The use according to claim 32, wherein the microorganism is a Gram negative or Gram positive bacterium.

34. The use according to claim 32 or 33, wherein the bacterium is MCR positive or MCR negative.

35. The use according to any one of claims 32 to 34, wherein the bacterium is carbapenem-resistant.

36. The use according to any one of claims 31 to 35, wherein the compound according to any one of claims 1 to 16 is used in conjunction with colistin.

37. A compound according to any one of claims 1 to 16 for use in therapy.

38. Use of a compound according to any one of claims 1 to 16 in the manufacture of a medicament for the treatment of a bacterial infection.

39. The use according to claim 38, wherein the compound according to any one of claims 1 to 16 is to be administered in conjunction with colistin.

40. The use according to claims 38 and 39, wherein the compound according to any one of claims 1 to 16 is present at an amount in the range of about 2 µg/mL to about 75 µg/mL.

41. The use according to claim 40, wherein the compound according to any one of claims 1 to 16 and colistin are present at an equal amount by weight, or the compound according to claim 1 to 16 is present in excess of about 1.5 to about 6 times of colistin by weight.

42. The use according to claim 41, wherein colistin is present at a range of about 1 mg/kg to about 10 mg/kg and the compound according to any one of claims 1 to 16 is present at a range of 10 mg/kg to about 50 mg/kg.

43. The use according to any one of claims 38 to 42, wherein the compound according to claims 1 to 16 is to be administered intramuscularly, intraperitoneally, topically, subcutaneously or intravenously.