Moreover, as the MCR gene is transferred via a plasmid mediated mechanism, lateral spread easily occurs among different strains of bacteria, and further worsening of the situation can be anticipated. More recently, three other mutations have been recognized, MCR-2, MCR-3 and MCR-4. However, the mechanism of action has been thus far a modification of Lipid A with the attachment of phosphoethanolamine to Lipid A (**Fig. 2**). Therefore, strategies to tackle the resistance conferred by MCR genes are in urgent need. Particularly affected are patients with carbapenamase resistant bacteria that are not sensitive to other antibiotics.

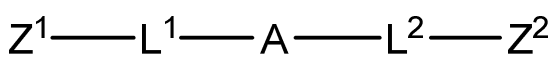
There is therefore a need for a new approach to tackling mcr-1 resistance that at least partially ameliorates the shortcomings above.

SUMMARY

A novel method for the design of new antibiotics or antibiotic adjuvants against MCR strains, including MCR-1, MCR-2, MCR-3 and MCR-4 has been developed. A library of molecules that perturb the hydrogen bonding network of the MCR modified outer membrane were designed. The approach combines a new *in silico* modeling method which greatly accelerates the development time while lowering the costs of new antimicrobial therapeutics. The method compares *in silico* designs with laboratory verification and in vivo tests of efficacy for the treatment of MCR infections.

The design method is based on fragment based pharmacostrategy and includes four steps: (i) *in silico* modeling for target identification; (ii) ligand design (iii) synthesis and (iv) biological validation. With one or more rounds of optimization, one of more lead compounds are revealed. For the MCR positive strains of Gram-negative bacteria, two targets were identified: the active site of MCR-1 protein and the hydrogen bonding network of the outer membrane. Based on the detailed atomistic analysis, a library of compounds that destabilized the outer membrane of *E. coli* with the mcr-1 plasmid was designed, which overcomes resistance and kills the bacteria. Several compounds were selected from the library and their MICs as well as their synergistic activity with colistin were tested. One of the compounds, GLA-DPA, displayed limited antimicrobial activity against a panel of clinically isolated colistin resistant bacteria. However, when combined with colistin, GLA-DPA was shown to restore the sensitivity of *E. coli* with mcr-1 to colistin. The effective dose of colistin, when combined with the disclosed compound, may therefore be lowered to a level that would obviate toxicity.

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



formula (I)

wherein A is a hydrophobic moiety;

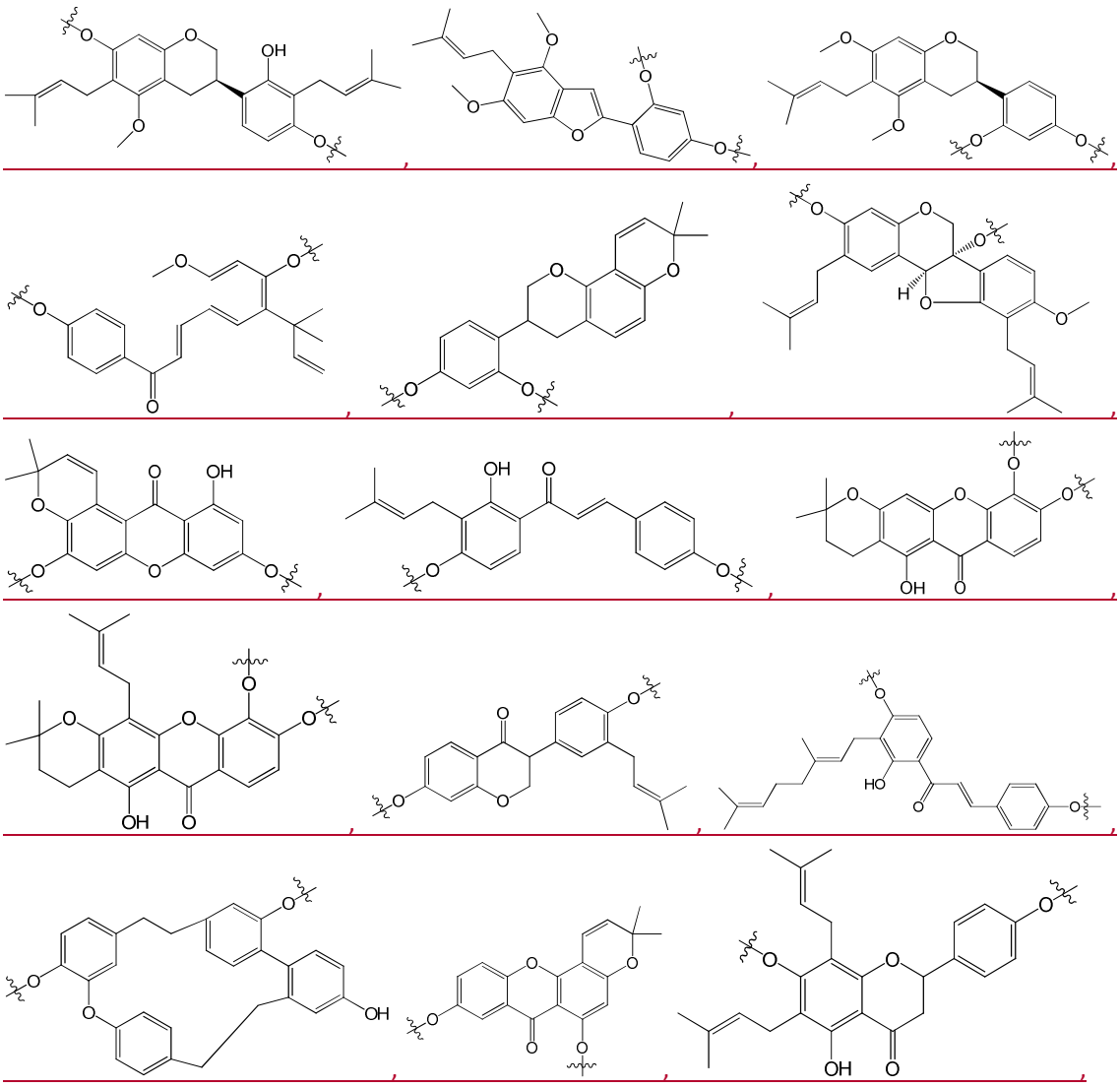
L^1 and L^2 are independently a linker; and

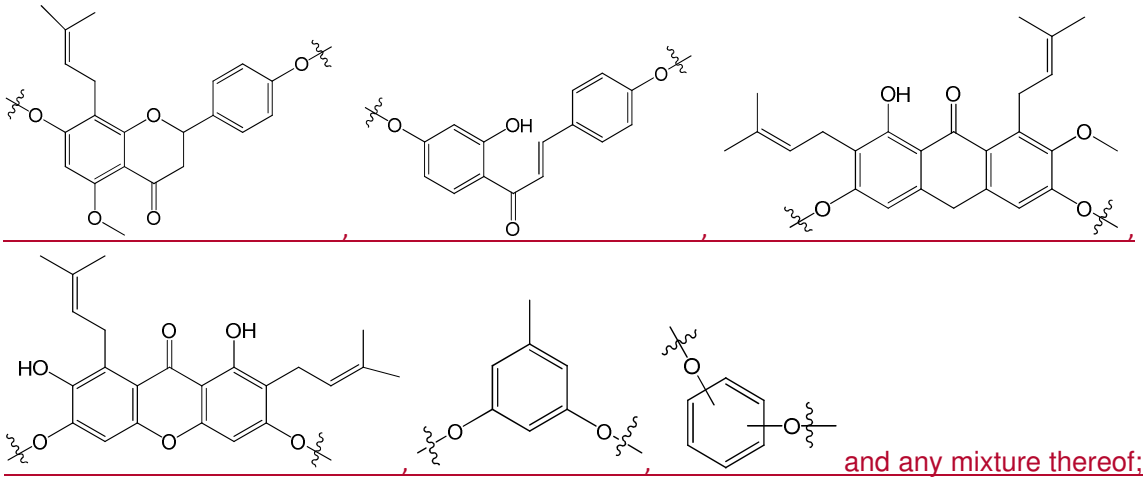
Z^1 and Z^2 are independently an N-containing moiety.

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:

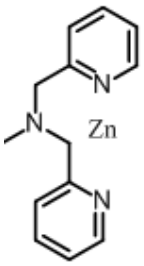




and any mixture thereof;

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

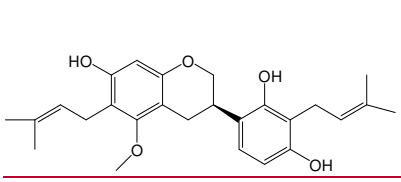
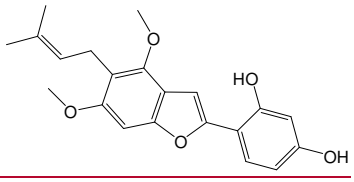
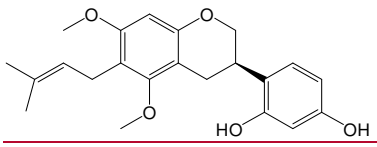
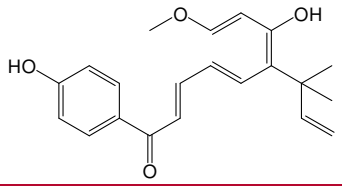
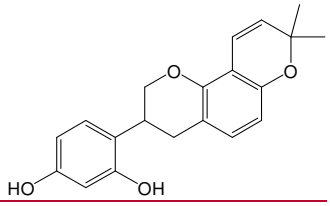
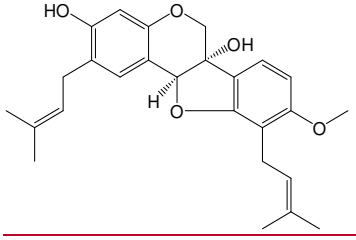
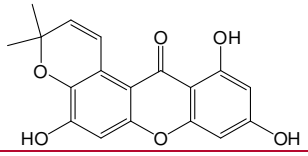
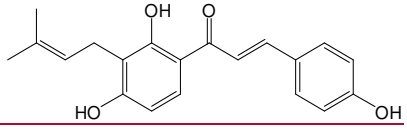
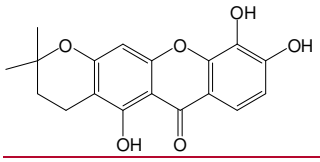
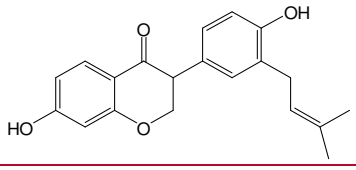
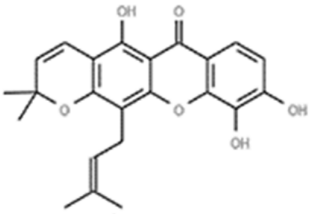
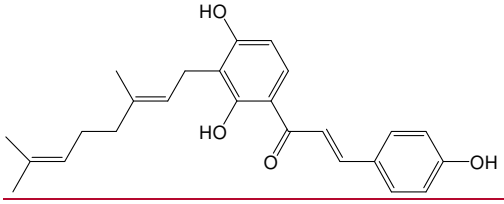
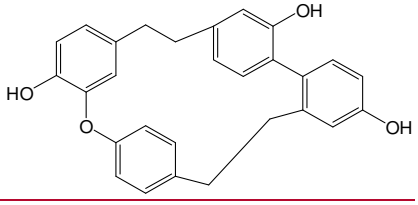
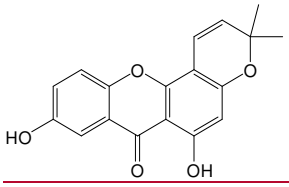
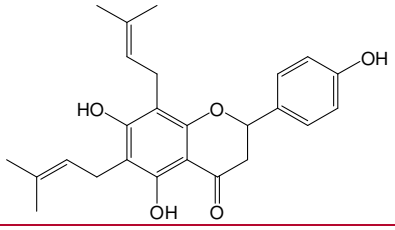
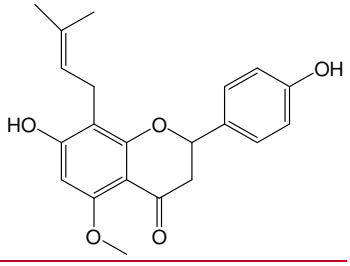
Advantageously, the N-containing moiety may disrupt the electrostatic interactions (e.g., the hydrogen bonding network) that stabilize the bacterial membrane. Advantageously, this may result in bacterial cell kill. Alternatively, the disruption of the hydrogen bonding network may facilitate other antibiotics 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.

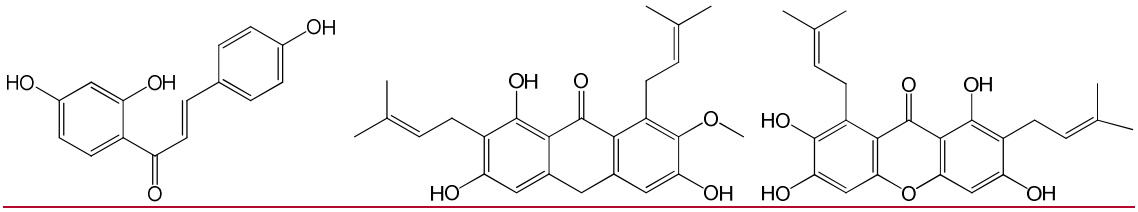
The compound of formula (I) may be effective in killing Gram positive bacteria alone or when co-administered with colistin. The compound of formula (I) may be effective in killing Gram negative bacteria that are MCR positive alone or when co-administered with colistin. In such a case, the N-containing 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.

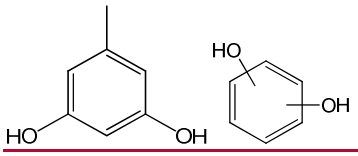
In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above, or a pharmaceutically acceptable salt or hydrate thereof, in association with a pharmaceutically acceptable carrier.

In another ~~aspect~~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 as defined above, comprising the step of contacting a hydrophobic moiety with an N-containing moiety under reaction conditions, wherein the hydrophobic moiety is selected from the group consisting of:





and any mixture thereof; and wherein the N-containing moiety is a dipicolylamine.

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

In another ~~aspect~~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 or inhibit the growth of a microorganism in vitro, wherein the compound 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 ~~aspect~~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.

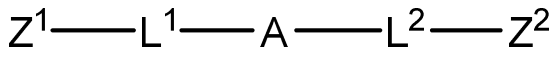
DEFINITIONS

"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,

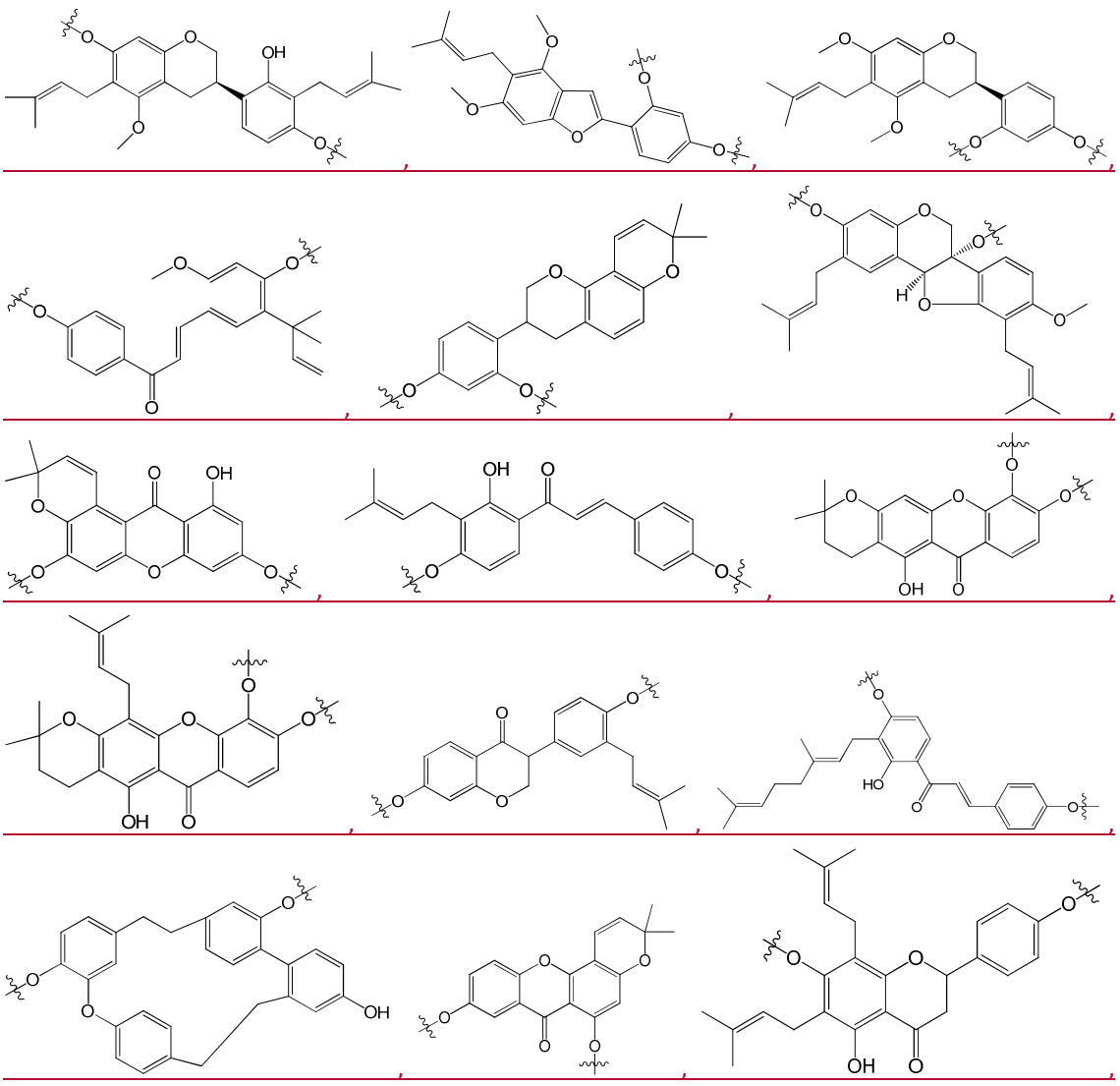
Claims

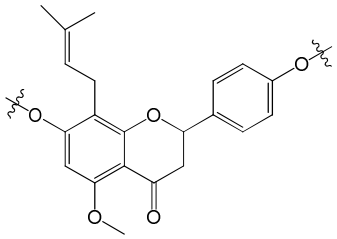
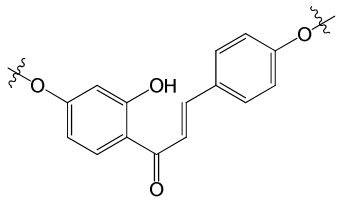
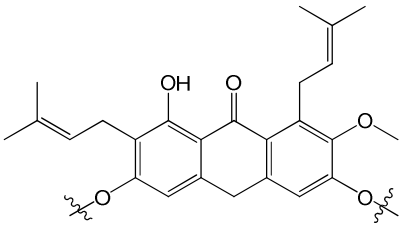
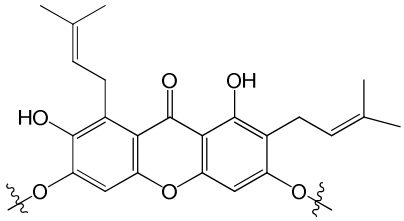
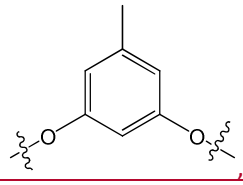
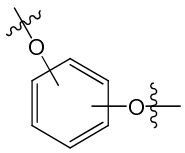
1. A compound having the following formula (I):



formula (I)

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

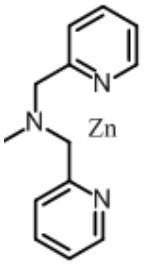


, , , , , and any mixture thereof;

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

Z^1 and Z^2 ~~are~~ independently ~~an N-containing moiety~~has the following structure:



,

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

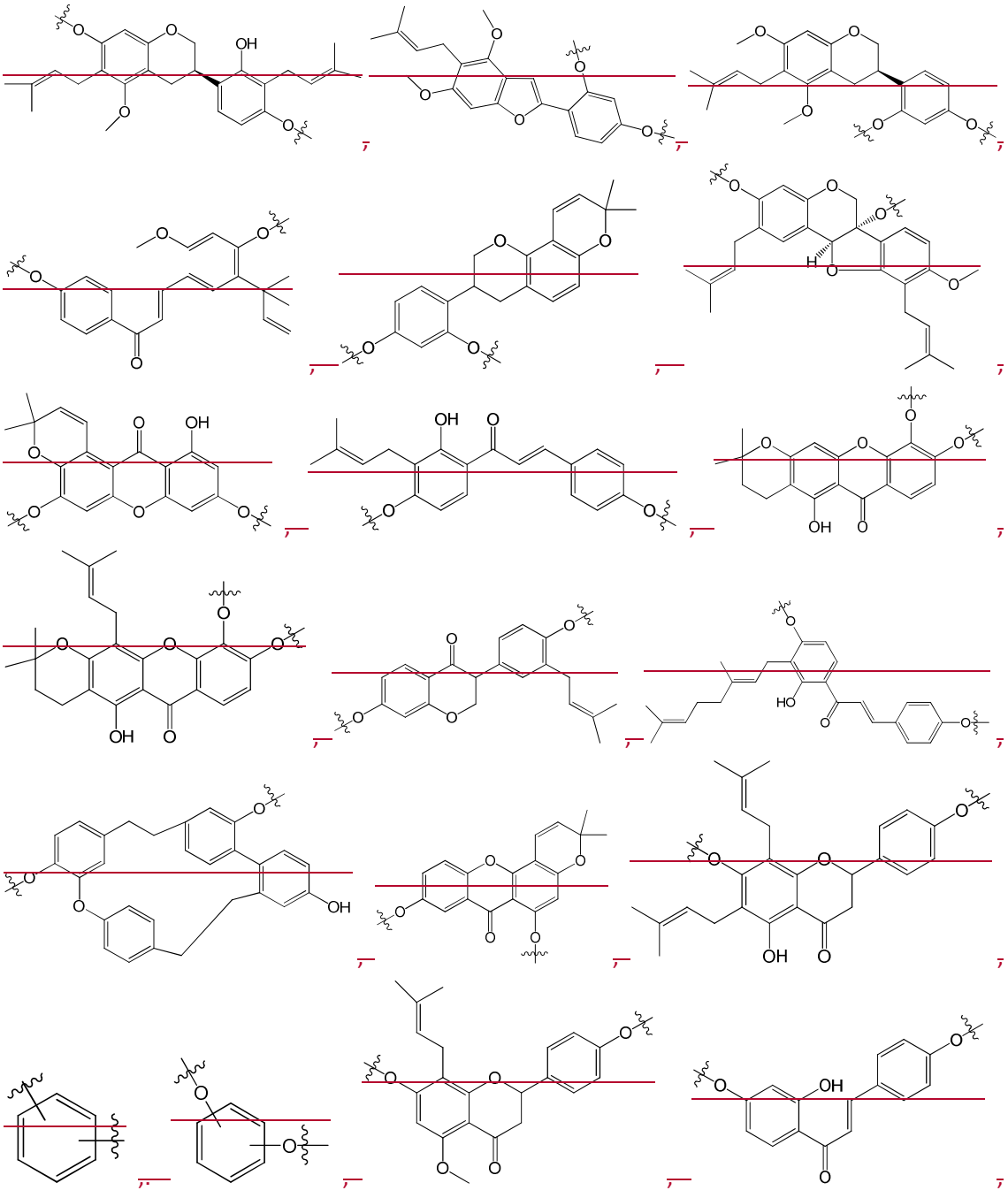
~~2. The compound according to claim 1, wherein A comprises at least one substituted or unsubstituted aryl.~~

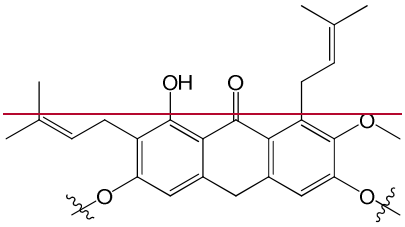
~~3. The compound according to claim 2, wherein A further comprises at least one alkenyl group.~~

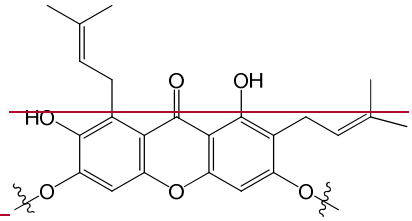
~~4. The compound according to claim 3, wherein A is planar or substantially planar.~~

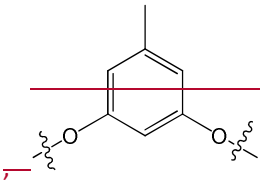
~~5. The compound according to claim 4, wherein A further comprises at least one isoprenyl group.~~

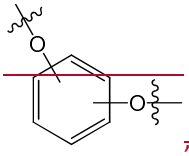
~~6. The compound according to any one of the preceding claims, wherein A is selected from the group consisting of:~~





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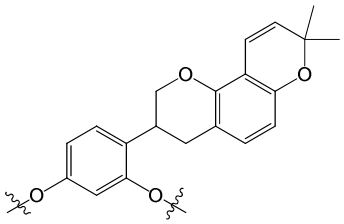
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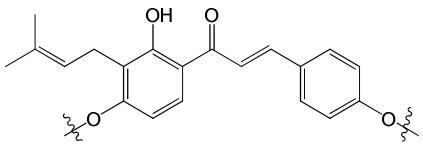
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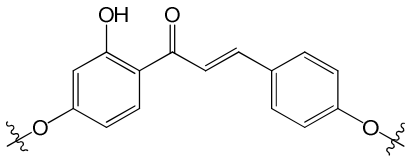
~~, and any mixture thereof,~~

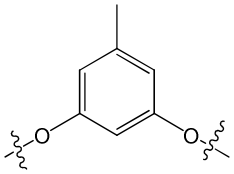
~~wherein the broken bond represents where the structure attaches to the remainder of formula (I).~~

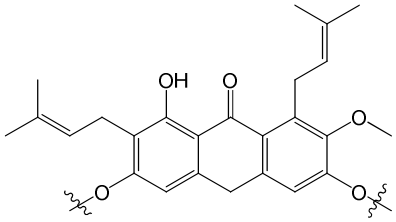
~~7~~2. The compound according to claim ~~6~~1, wherein A is selected from the group consisting of:

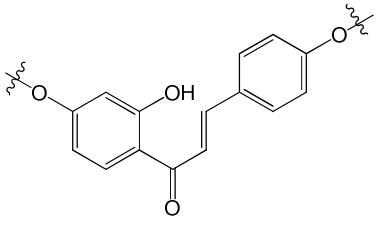


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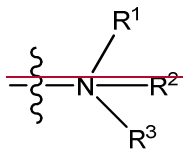
, 



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

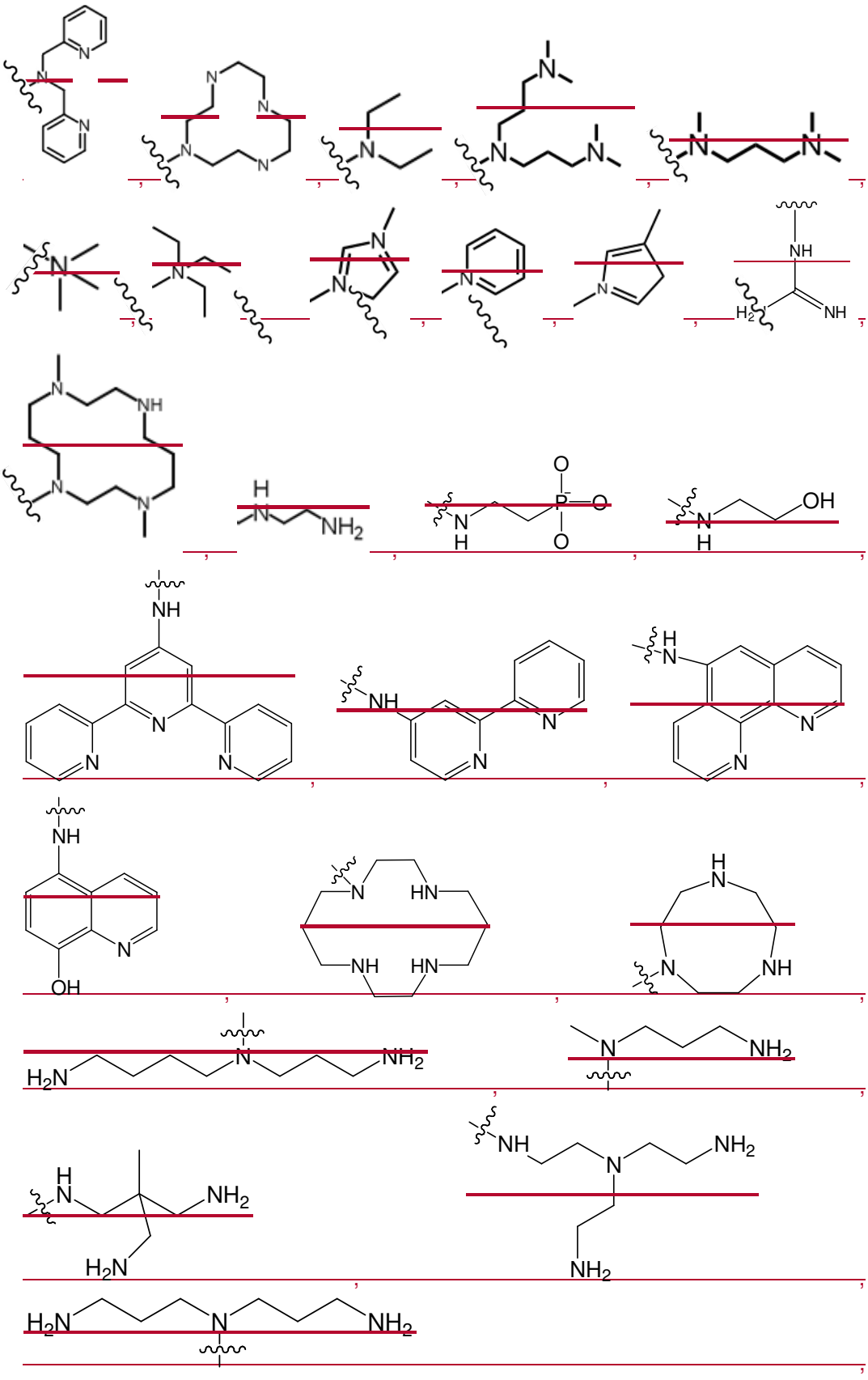
R^3 is absent or hydrogen, or substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aminoalkyl, guanidine, substituted or unsubstituted guanidylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted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

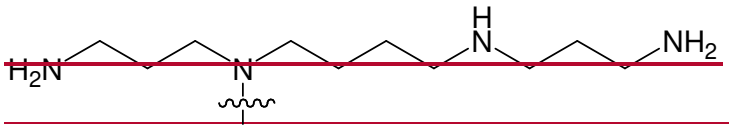
wherein when R^3 is present, the nitrogen atom is a cationic quaternary nitrogen.

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.

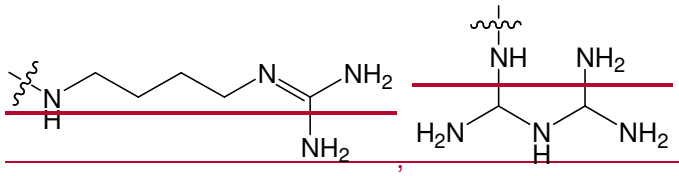
11. The compound according to claim 9 or 10, wherein R^1, R^2 and R^3 are independently selected from the group consisting of methyl, ethyl, propyl, butyl, $-(CH_2)_xNR'R''$, $-(CH_2)_xOH$, $-(CH_2)_xPO_3$, $-(CH_2)_xCR'R''R'''$, $-(C(NH_2)NHC(NH_2))x\text{-}NH_2$, guanidine, 2-methylpyridine, 1-methylimidazole, 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:



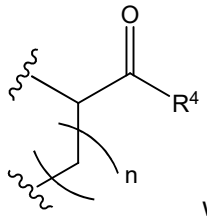


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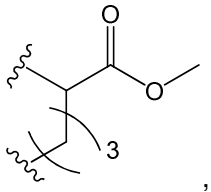
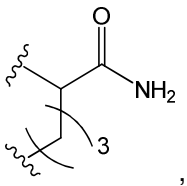
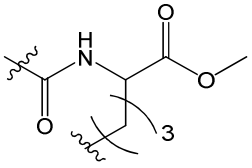
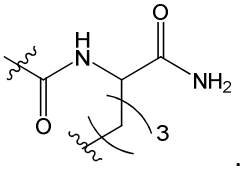


, and any combination thereof.

313. 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:

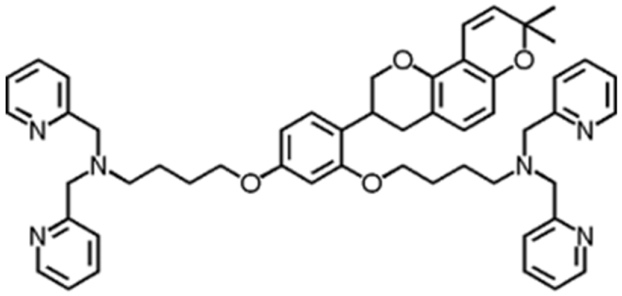


wherein n is an integer from 1 to 10 and R^4 is an amino or a heteroalkyl and the broken bond represents where the structure attaches to the remainder of formula (I).

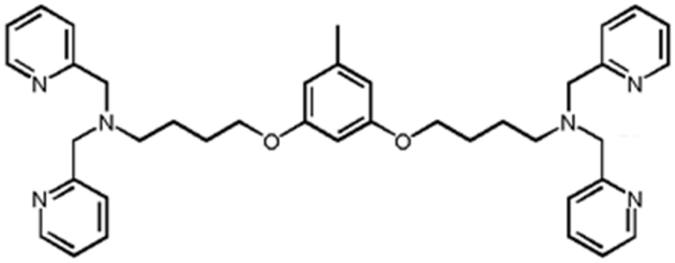
144. The compound according to claim 133, wherein L^1 and L^2 are independently selected from the group consisting of $-(CH_2)_4-$, amide, , , and any combination thereof, or  and .

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

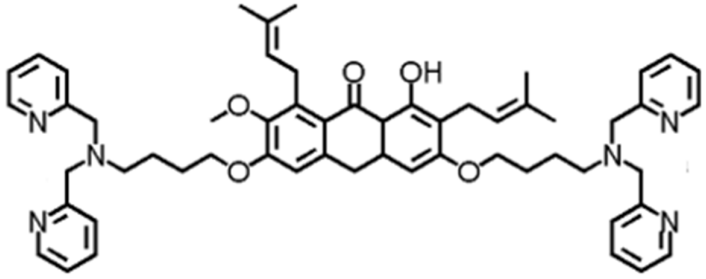
16. The compound according to any one of the preceding claims, wherein the compound of formula (I) has the following structure:



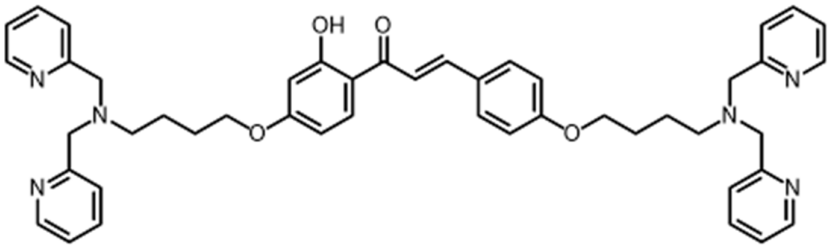
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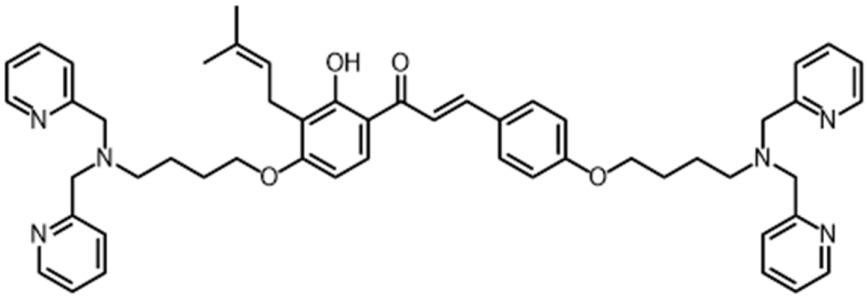
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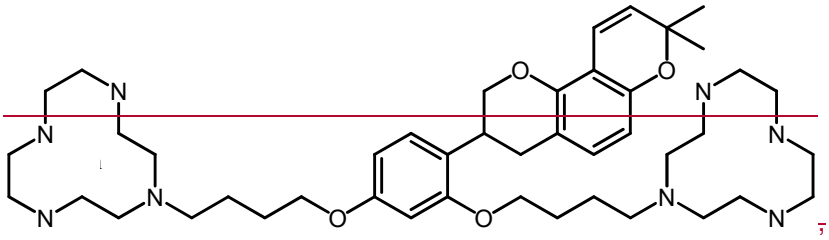


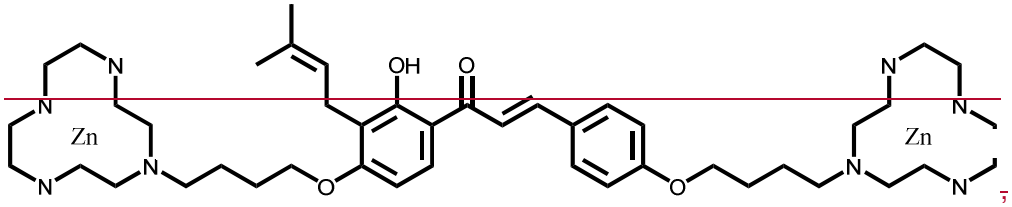
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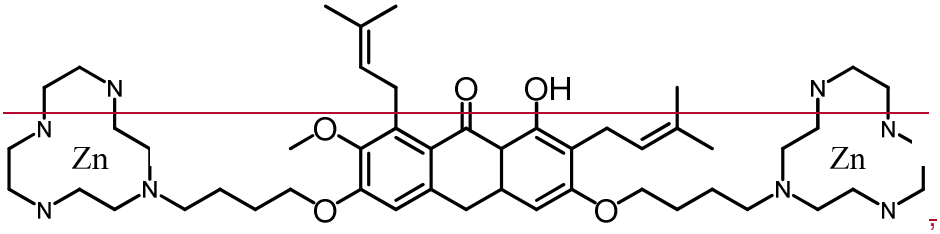


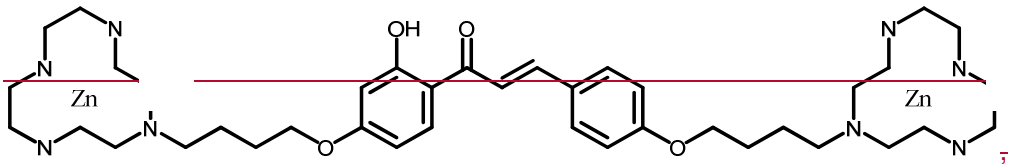
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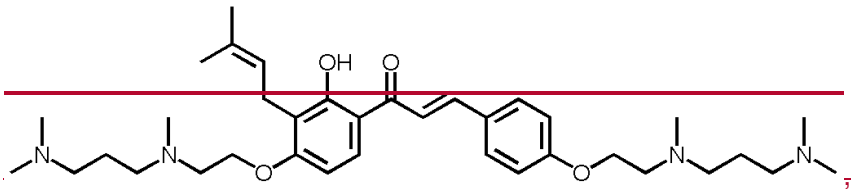


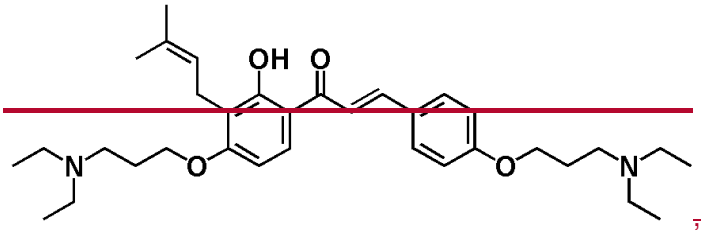


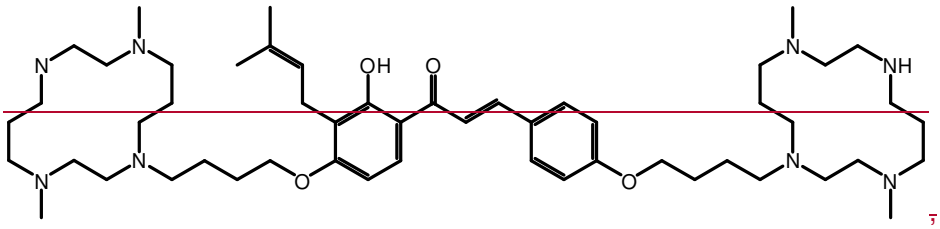


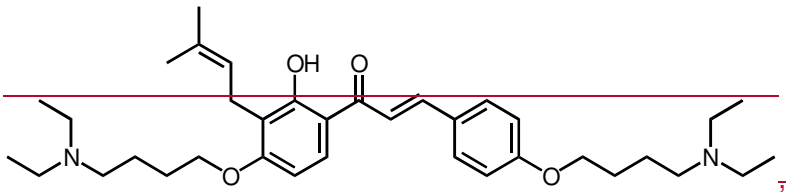


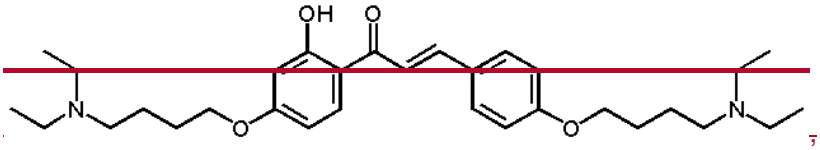


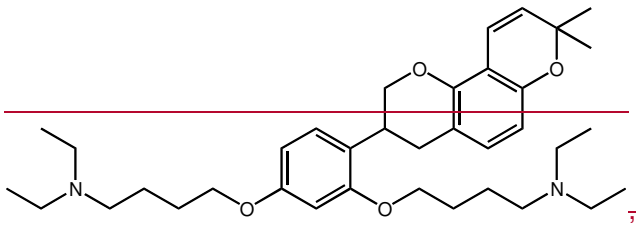


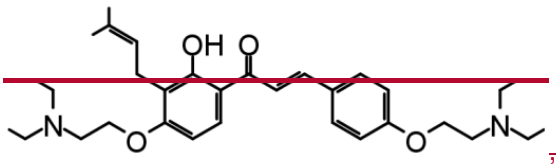


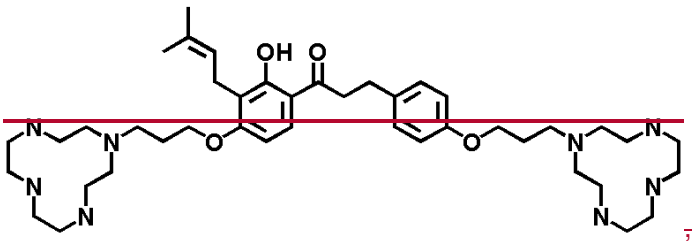


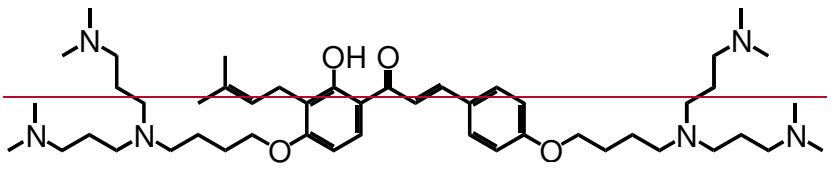


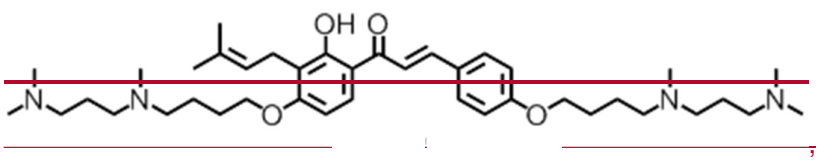


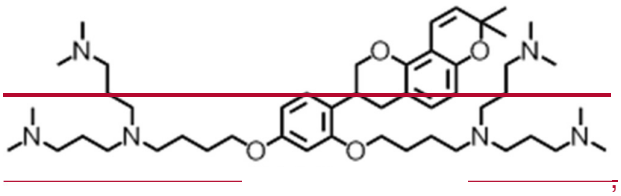


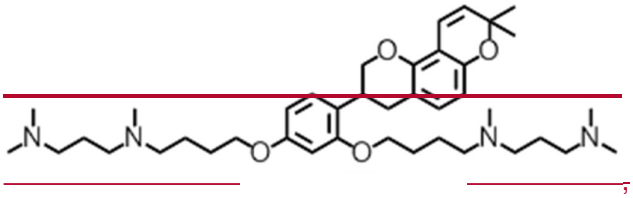


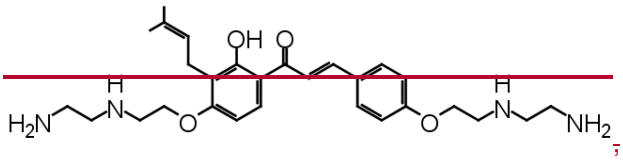


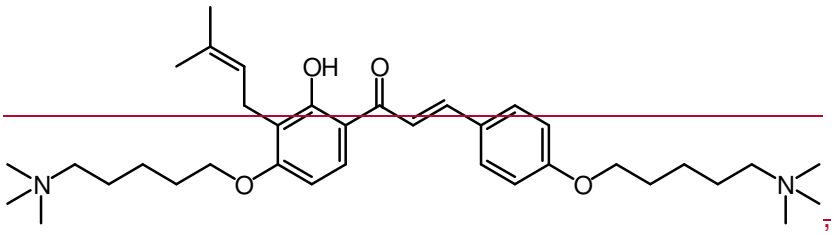


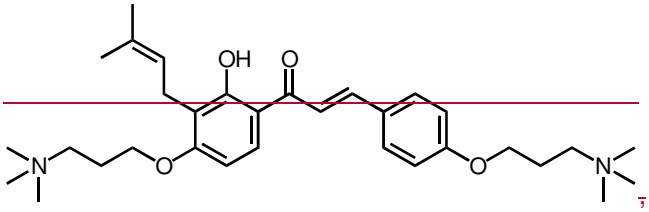


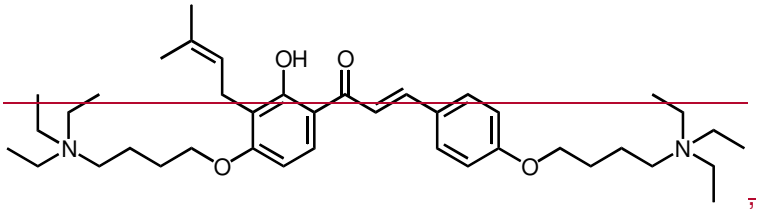


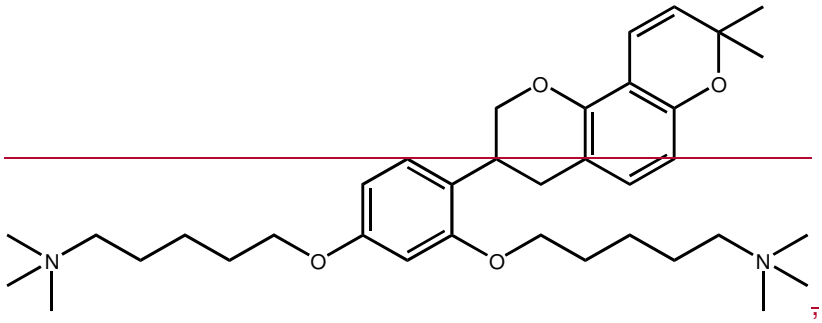


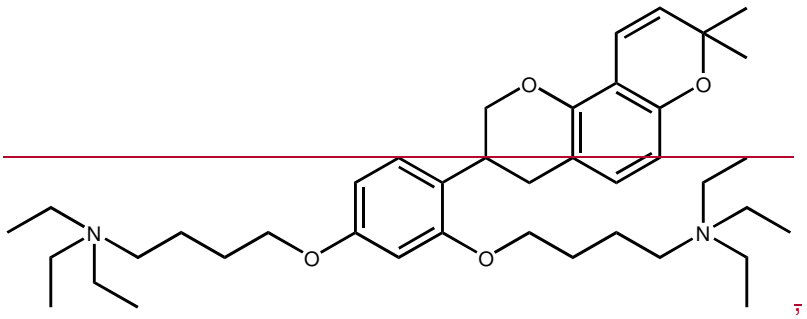




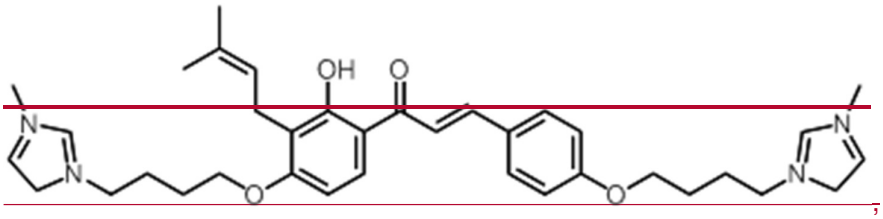




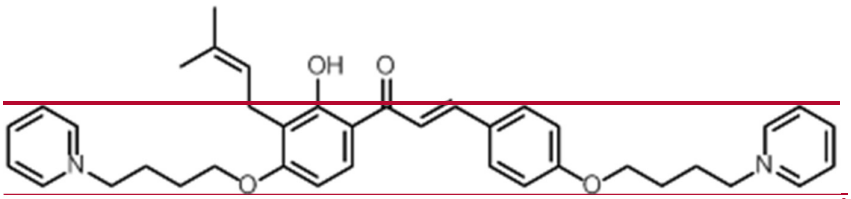



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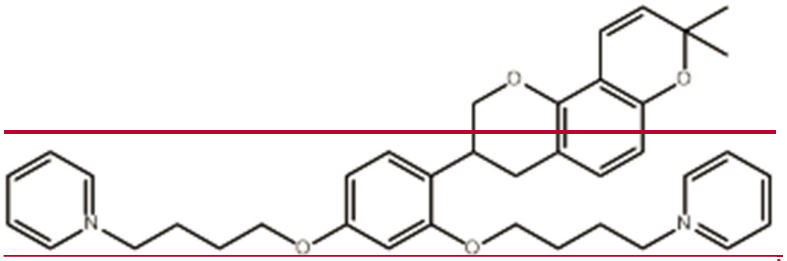
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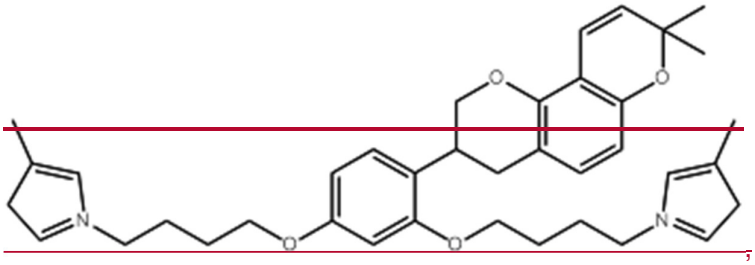
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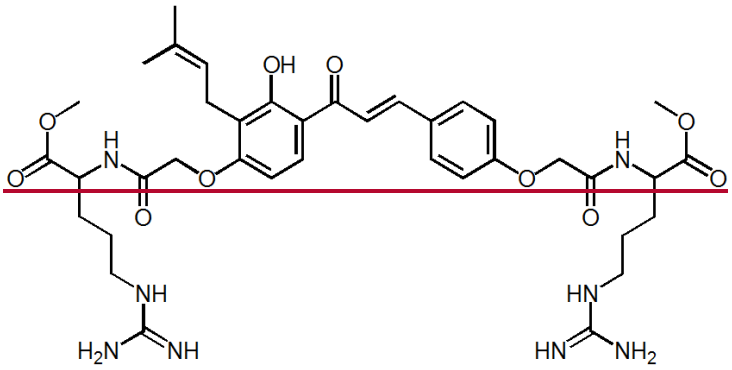
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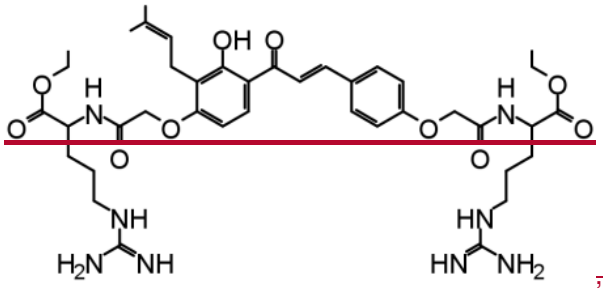

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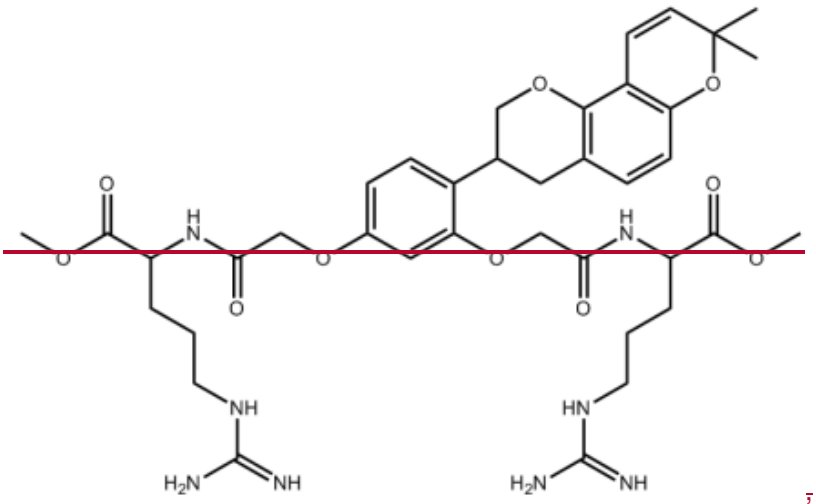
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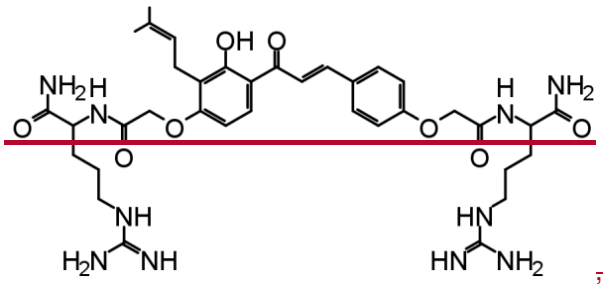

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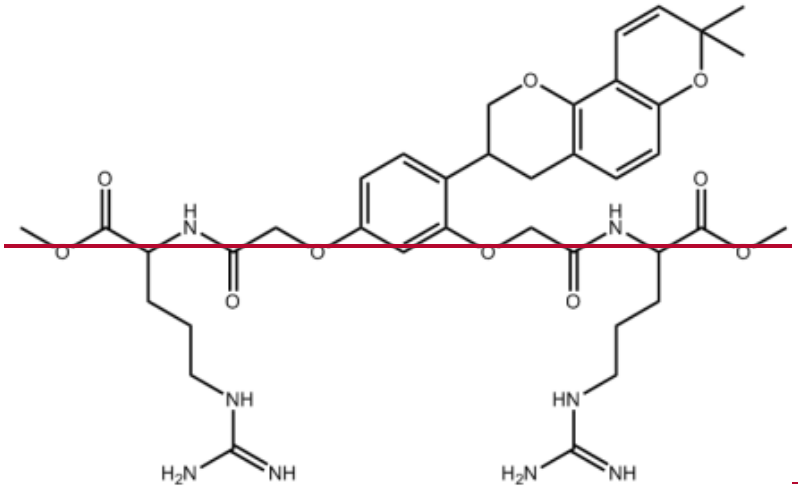
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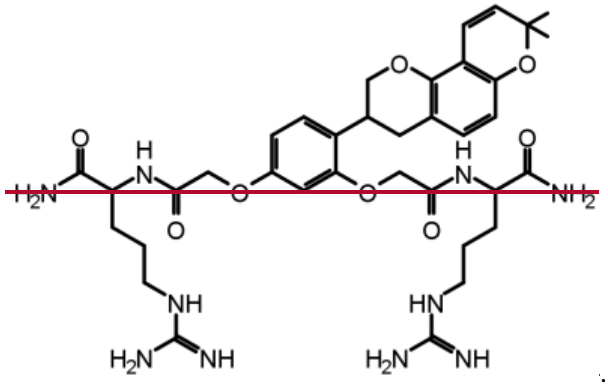








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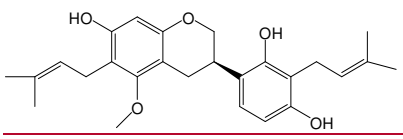
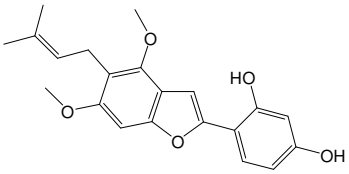
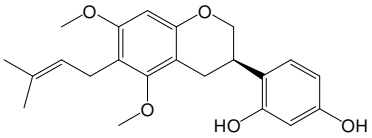
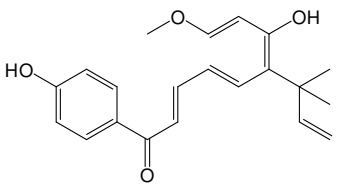
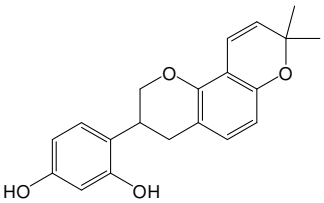
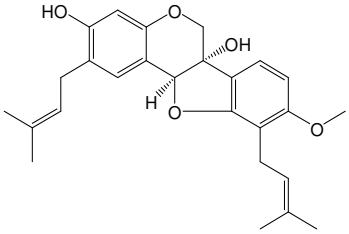
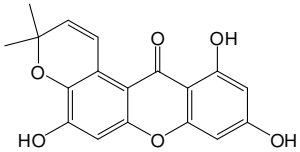
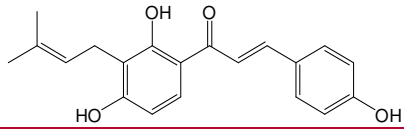
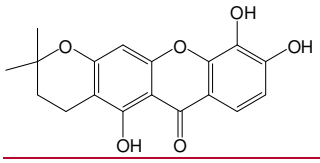
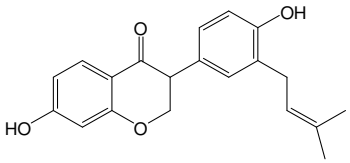
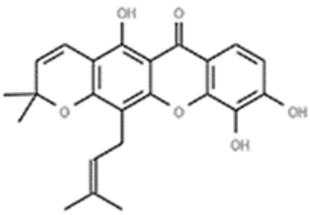
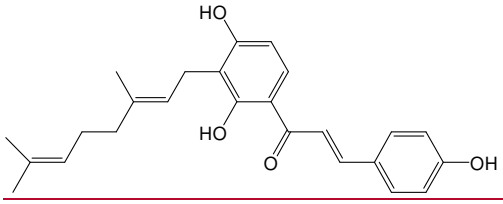
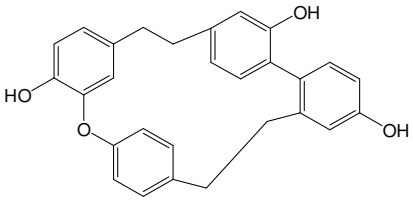
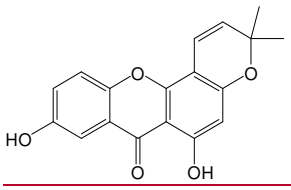
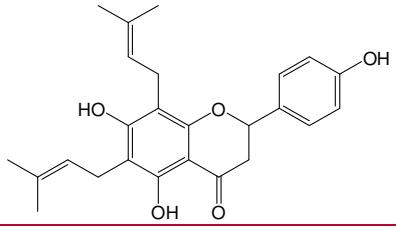
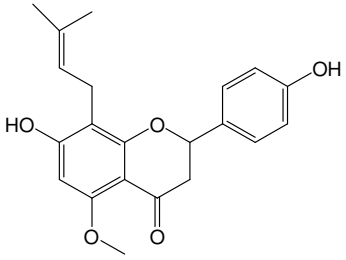
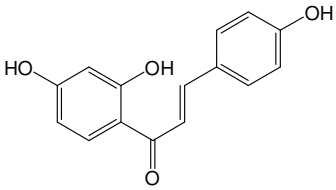
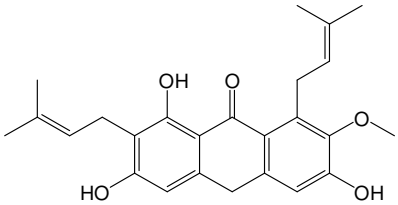
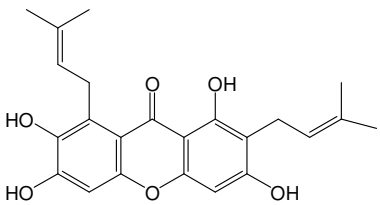
~~1~~7. The compound according to any one of the preceding claims, wherein each N-containing moiety is independently chelated to zinc.

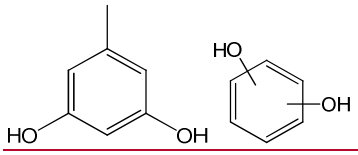
~~1~~8. The compound according to any one of the preceding claims, wherein each N-containing moiety independently has a positive charge.

~~1~~9. 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.

1~~2~~0. The pharmaceutically composition according to claim ~~1~~9, wherein the pharmaceutically acceptable carrier is saline.

~~2~~11. A process for preparing a compound according to any one of claims 1 to ~~1~~8, comprising the step of contacting a hydrophobic moiety with an N-containing moiety under reaction conditions, wherein the hydrophobic moiety is selected from the group consisting of:

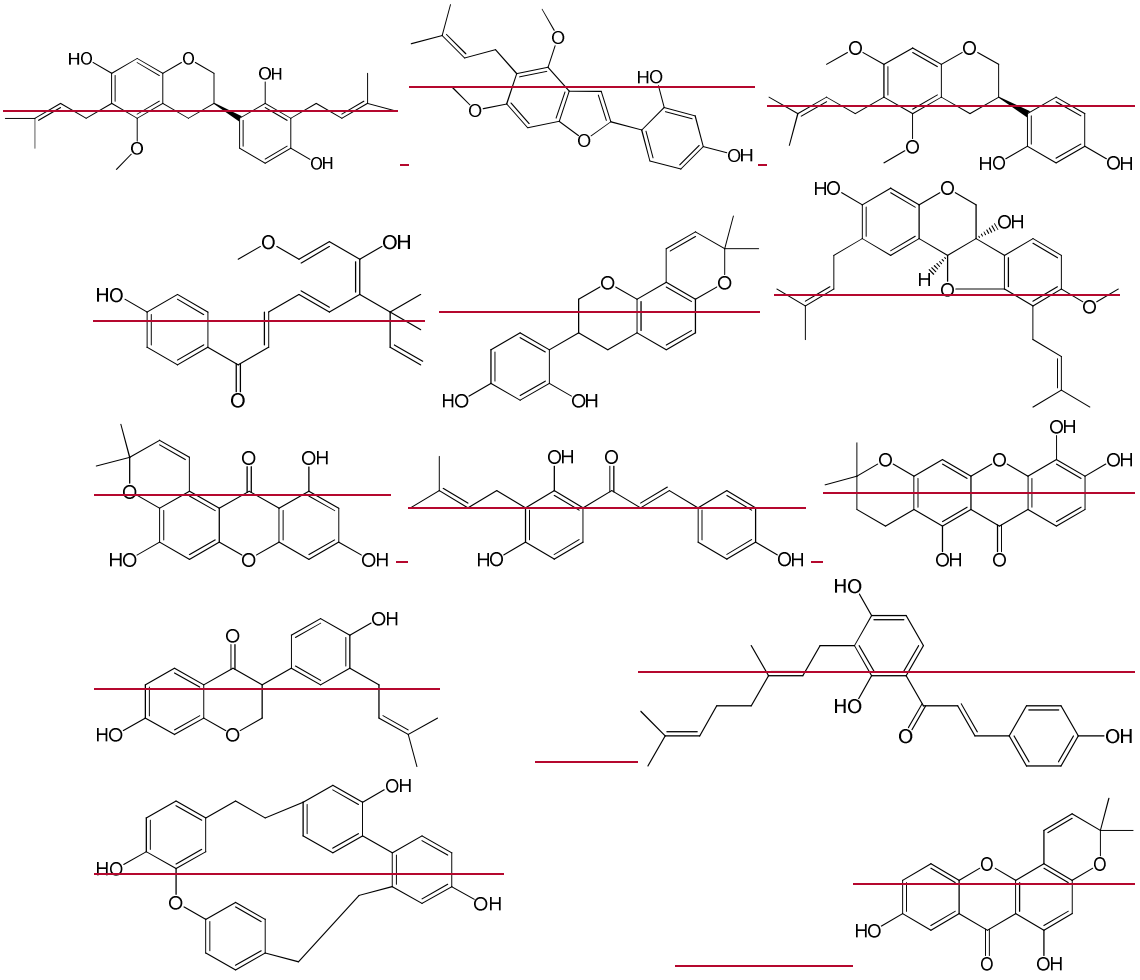


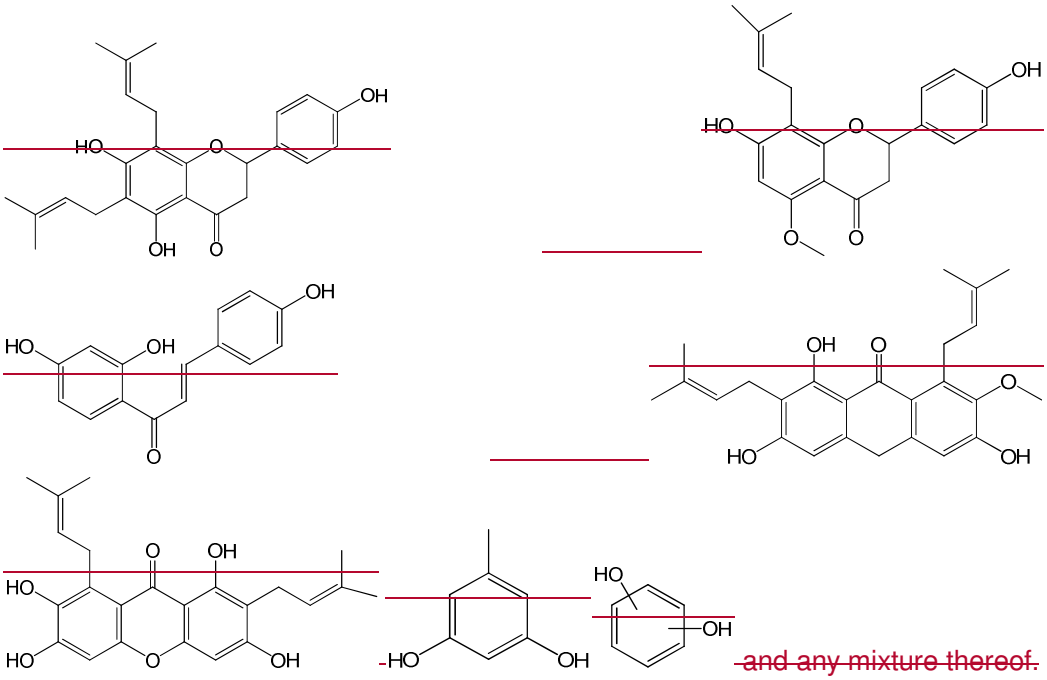
and any mixture thereof; and wherein the N-containing moiety is a dipicolylamine.

~~2~~12. The process according to claim 1~~2~~1, further comprising the step of contacting the hydrophobic moiety with a linker before contacting with the N-containing moiety.

~~23~~13. The process according to claim ~~21~~ 11 or ~~22~~12, 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~~14. The process according to any one of claims ~~21 –~~11 to ~~24~~13, 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.~~

15~~27~~. The process according to any one of claims ~~21 –~~11 to ~~26~~14, comprising the step of adding zinc after the N-containing moiety is covalently bonded to the linker or hydrophobic moiety.

~~28~~16. The process according to any one of claims ~~21 –~~11 to ~~27~~15, 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~~17. The process according to any one of claims ~~21 –~~11 to ~~28~~16, wherein the contacting step is performed at a temperature in the range of ~~about~~ 21 °C to ~~about~~ 160 °C.

~~30~~18. The process according to any one of claims ~~21 –~~11 to ~~29~~17, wherein the contacting step is performed for a duration in the range of ~~about~~ 2 hours to ~~about~~ 36 hours.

~~31~~19. Use of the compound according to any one of claims 1 to ~~1~~6 or the pharmaceutical composition according to claim ~~1~~9 or ~~2~~10, to kill or inhibit the growth of a microorganism in vitro, wherein the compound according to any one of claims 1 to 6 is used in conjunction with colistin.

~~32~~20. The use according to claim ~~31~~19, wherein the microorganism is a bacterium, archaea, fungus, protist, or any mixture thereof.

~~33~~21. The use according to claim ~~32~~20, wherein the microorganism is a Gram negative or Gram positive bacterium.

~~34~~22. The use according to claim ~~32~~ 20 or ~~33~~21, wherein the bacterium is MCR positive or MCR negative.

~~35~~23. The use according to any one of claims ~~32~~ 20 to ~~34~~22, 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~~24. A compound according to any one of claims 1 to ~~1~~6 for use in therapy.

~~38~~25. Use of a compound according to any one of claims 1 to ~~1~~6 in the manufacture of a medicament for the treatment of a bacterial infection, wherein the compound according to any one of claims 1 to 6 is to be administered in conjunction with colistin.

~~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~~26. The use according to claim~~s~~ ~~38 and 39~~25, wherein the compound according to any one of claims 1 to ~~1~~6 is present at an amount in the range of ~~about~~ 2 µg/mL to ~~about~~ 75 µg/mL.

~~41~~27. The use according to claim ~~40~~26, wherein the compound according to any one of claims 1 to ~~1~~6 and colistin are present at an equal amount by weight, or the compound according to claim 1 to ~~1~~6 is present in excess of ~~about~~ 1.5 to ~~about~~ 6 times of colistin by weight.

~~42~~28. The use according to claim ~~41~~27, 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 ~~1~~6 is present at a range of 10 mg/kg to ~~about~~ 50 mg/kg.

~~43~~29. The use according to any one of claims 27~~38~~ to ~~42~~28, wherein the compound according to claims 1 to ~~1~~6 is to be administered intramuscularly, intraperitoneally, topically, subcutaneously or intravenously.