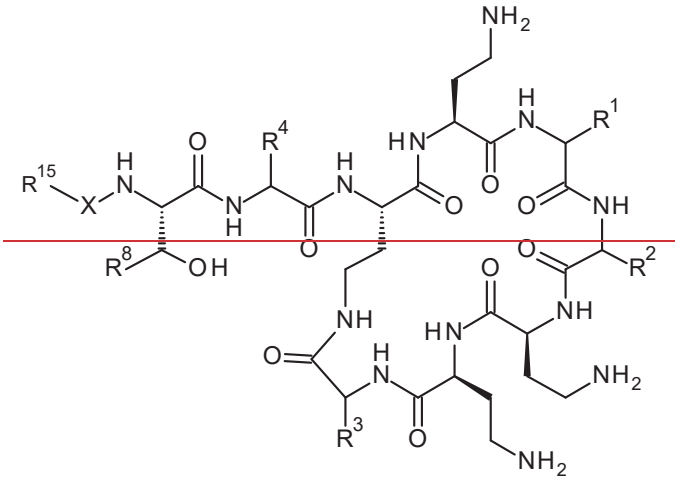
Summary

In a general example, the disclosure provides compounds having a deacylated polymyxin core, such as a nonapetide core of Polymyxin B or Colistin with the amino acid residue at position 3 substituted with Dap, having a group -X-R^{15}, as defined herein, at its N terminal. Such compounds find use in a method of treatment or prophylaxis, optionally in combination with a second active agent. The compounds may be used to treat a microbial infection, such as a Gram-negative bacterial infection.

The compounds of the present disclosure are shown to have low cytotoxicity balanced with acceptable kidney drug levels after parenteral dosing. The compounds of the present disclosure are shown to be superior to both Polymyxin B, as well as modified polymyxin compounds known in the art, including those previously reported by the present applicant. This superiority is manifest in one or more of the following characteristics: lower cytotoxicity, acceptable kidney drug levels (i.e., acceptable renal toxicity, resulting from kidney drug levels are not high) after parenteral dosing, efficacy in mouse thigh and lung models, and/or superior MIC against pathogenic bacterial strains, while being equivalent to the prior art compounds in the others.

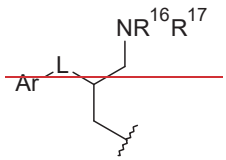
Typically the compounds known in the art exhibit one, or perhaps two of these advantageous characteristics, but not all. For example, it is now relatively common to find polymyxin compounds having lower cytotoxicity, but this lower cytotoxicity is often accompanied with a reduction in antibacterial activity. Further, compounds having a lower cytotoxicity may nevertheless be found within the kidney at high levels after dosing. Such compounds are therefore still toxic, and not useful in methods of medical treatment.

~~In one aspect, the present disclosure refers to a compound of formula (I):~~



~~wherein:~~

~~-X- represents -C(O)-;~~
~~-R^1 together with the carbonyl group and nitrogen alpha to the carbon to which it is attached, is phenylalanine, leucine, norleucine, valine or norvaline residue;~~
~~-R^2 is C_{1-4} alkyl optionally substituted with one hydroxyl group;~~
~~-R^3 together with the carbonyl group and nitrogen alpha to the carbon to which it is attached, is a threonine residue;~~
~~-R^4 together with the carbonyl group and nitrogen alpha to the carbon to which it is attached, is Dap;~~
~~-R^8 is hydrogen or methyl; and~~
~~-R^{15} is a group:~~

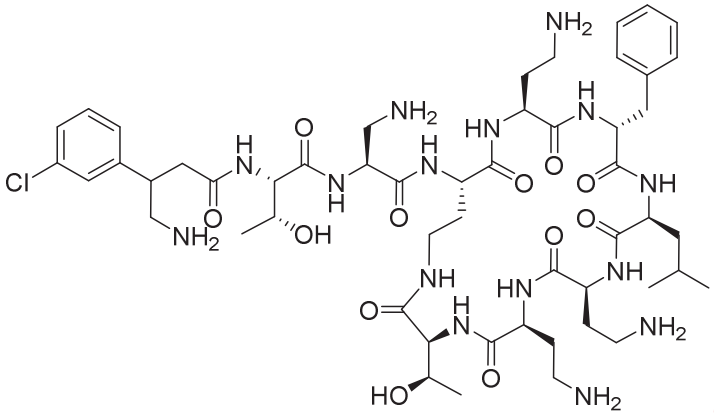


~~where:~~

~~-R^{16} is hydrogen;~~
~~-R^{17} is hydrogen;~~

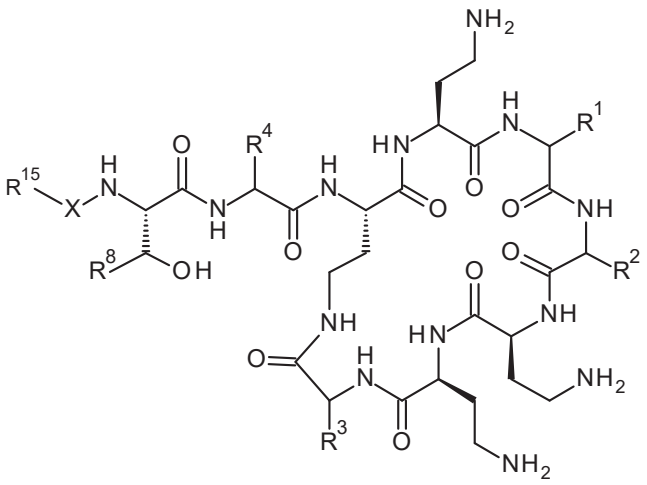
~~-L- is a covalent bond or methylene;~~
~~-Ar is optionally substituted aryl~~

~~and salts, solvates and protected forms thereof~~ In one aspect, the present disclosure refers to a compound of formula (II):



and salts, solvates and protected forms thereof.

In a first example of the disclosure, there is provided a compound of formula (I), and pharmaceutically acceptable salts, solvates, protected forms and prodrug forms thereof. The compound of formula (I) is represented thus:



wherein:

In another aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as disclosed herein, optionally together with together with one or more pharmaceutically acceptable carriers.

The disclosure also provides a pharmaceutical composition comprising a compound of formula (I), optionally together with one or more pharmaceutically acceptable carriers.

In yet another aspect, the present disclosure refers to a compound as disclosed herein or a pharmaceutical composition as disclosed herein for use as a medicament ~~or prophylaxis~~.

In a further example there is provided a compound of formula (I), or a pharmaceutical composition comprising a compound of formula (I), for use in a method of treatment or prophylaxis.

In yet another aspect, the present disclosure refers to use of a compound as disclosed herein or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a microbial infection, , wherein the microbial infection is a Gram-negative bacterial infection.~~such as a bacterial infection~~

In yet a further example there is provided a compound of formula (I), or a pharmaceutical composition comprising a compound of formula (I), for use in a method of treating a microbial infection.

The present disclosure also provides a method of treatment, the method comprising the step of administering a compound of formula (I), or a pharmaceutical composition comprising a compound of formula (I), to a subject in need thereof. The method may be for the treatment of a microbial infection.

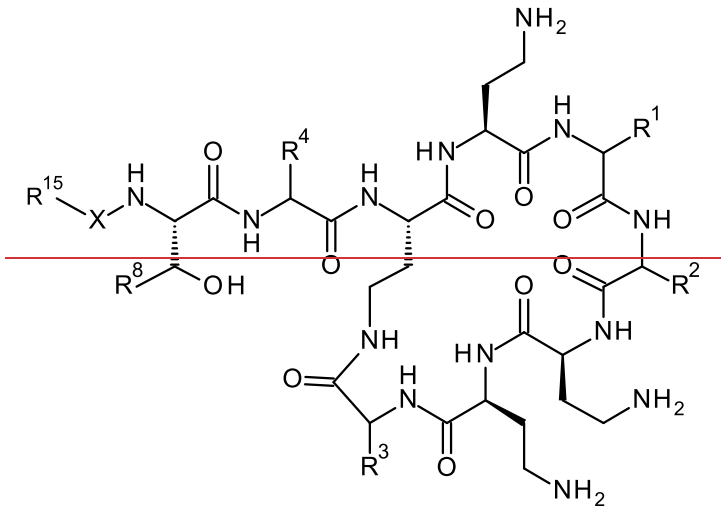
A microbial infection may be a bacterial infection, such as a Gram-negative bacterial infection. The Gram-negative bacterial infection may be selected from the group consisting of *Escherichia* spp., *Klebsiella* spp., *Enterobacter* spp., *Salmonella* spp., *Shigella* spp., *Citrobacter* spp., and other Enterobacteriaceae, *Pseudomonas* spp., *Acinetobacter* spp., *Stenotrophomonas*, and *Legionella.*

The present disclosure also provides methods for the preparation of compounds of formula (I) as well as intermediate compounds for use in the preparation of the compounds of formula (I).

These and other aspects and embodiments of the disclosure are described in further detail below.

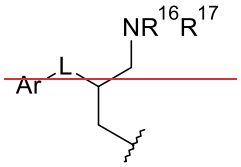
Claims:

1. A compound of formula (I):



wherein:

-X- represents -C(O)-;
-R^1 together with the carbonyl group and nitrogen alpha to the carbon to which it is attached, is phenylalanine, leucine, norleucine, valine or norvaline residue;
-R^2 is C_{1-4} alkyl optionally substituted with one hydroxyl group;
-R^3 together with the carbonyl group and nitrogen alpha to the carbon to which it is attached, is a threonine residue;
-R^4 together with the carbonyl group and nitrogen alpha to the carbon to which it is attached, is Dap;
-R^8 is hydrogen or methyl; and
-R^{15} is a group:



where:

-R^{16} is hydrogen;
-R^{17} is hydrogen;

-L- is a covalent bond or methylene;
-Ar is optionally substituted aryl

and salts, solvates and protected forms thereof.

2. The compound according to claim 1 or claim 2, wherein -R^1, together with the carbonyl group and nitrogen alpha to the carbon to which it is attached, is a phenylalanine or leucine residue, such as a phenylalanine residue.

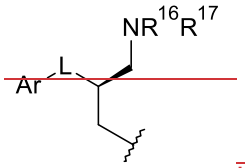
3. The compound according to claim 1 or claim 2, wherein -R^2, together with the carbonyl group and nitrogen alpha to the carbon to which it is attached, is a leucine, aminobutyrate, iso-leucine, threonine, valine or nor-valine residue.

4. The compound according to claim 3, wherein -R^2, together with the carbonyl group and nitrogen alpha to the carbon to which it is attached, is a leucine or aminobutyrate residue, such as a leucine residue.

5. The compound according to any one of the preceding claims, wherein -R^4 together with the carbonyl group and nitrogen alpha to the carbon to which it is attached, is L-Dap

6. The compound according to any one of the preceding claims, wherein -R^8 is methyl.

7. The compound according to any one of the preceding claims, wherein -R^{15} is:



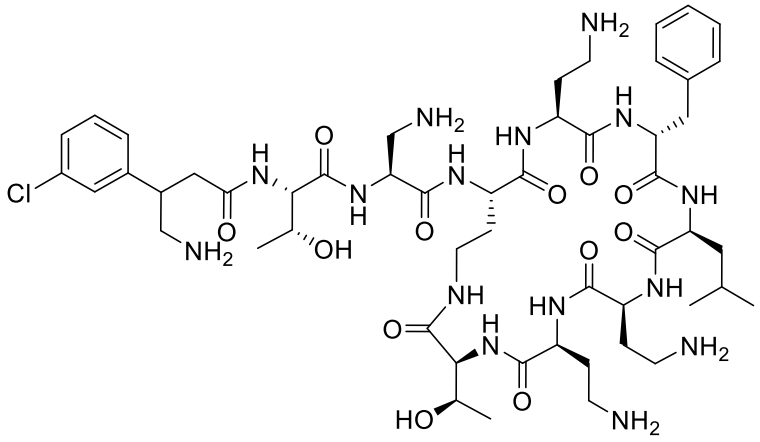
8. The compound according to any one of the preceding claims, wherein -L- is a covalent bond.

9. The compound according to any one of the preceding claims, wherein -Ar is optionally substituted phenyl.

10. The compound according to claim 9, wherein the phenyl is substituted with one or two groups -R^S, where each -R^S is independently selected from halo, alkyl, haloalkyl and aryl.

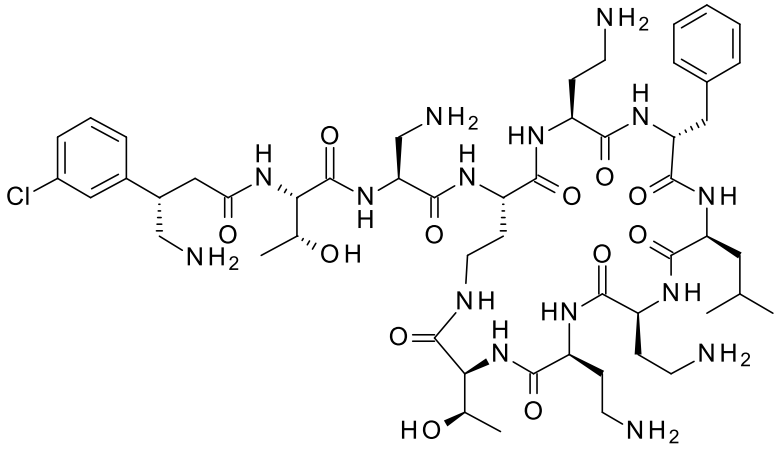
11. The compound according to claim 9, wherein the phenyl is substituted with one or two groups -R^S, where each -R^S is independently selected from chloro, propyl, phenyl and thiophenyl.

~~121~~. A compound of formula (I~~I~~) ~~according to claim 1, which is a compound of formula (II)~~:



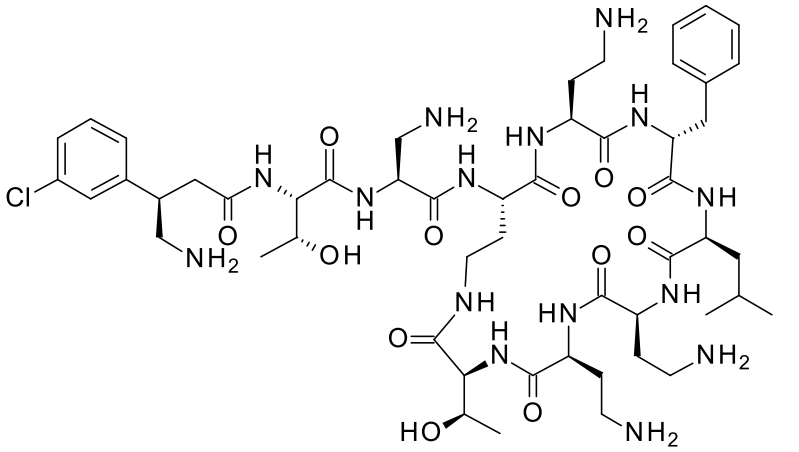
and salts, solvates and protected forms thereof.

~~132~~. ~~A~~ The compound of formula (I~~I~~) according to claim 1, which is a compound ~~of formula (II)~~:



and salts, solvates and protected forms thereof.

3. A compound of formula (II) according to claim 1, which is a compound:



and salts, solvates and protected forms thereof.

~~14~~4. A pharmaceutical composition comprising a compound according to any one of claims 1 to ~~1~~3, optionally together with ~~together with~~ one or more pharmaceutically acceptable carriers.

~~15~~5. A compound according to any one of claims 1 to ~~1~~3 or a pharmaceutical composition according to claim ~~1~~4 for use as a medicament ~~or prophylaxis~~.

~~16~~6. Use of a compound according to any one of claims 1 to ~~1~~3 or a pharmaceutical composition according to claim ~~1~~4 in the manufacture of a medicament for treating a microbial infection, ~~such as a bacterial infection.~~

~~17. The use according to claim 16,~~ wherein the microbial infection is a Gram-negative bacterial infection.~~,~~

7. The use of claim 6, wherein the Gram-negative bacterial infection is ~~such as~~ an infection by a Gram-negative bacteria selected from the group consisting of *Escherichia* spp., *Klebsiella* spp., *Enterobacter* spp., *Salmonella* spp., *Shigella* spp., *Citrobacter* spp., *Morganella morganii*, *Yersinia pseudotuberculosis* and other Enterobacteriaceae, *Pseudomonas* spp., *Acinetobacter* spp., *Moraxella*, *Helicobacter*, *Stenotrophomonas*, *Bdellovibrio*, acetic acid bacteria, *Legionella* and alpha-proteobacteria.