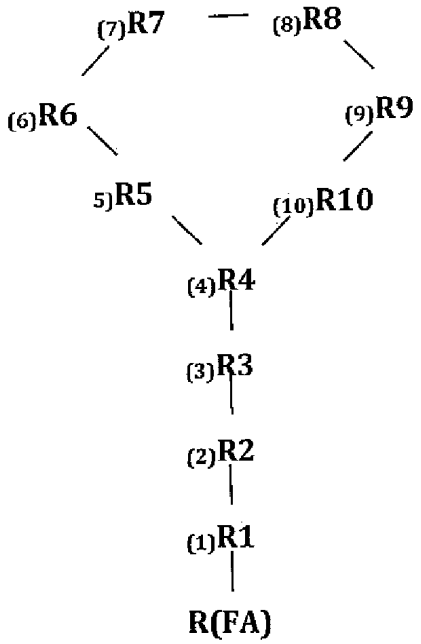
cial effects on patient survival. According to recent studies, the nephrotoxicity rate of polymyxin B and colistin (liberated from colistin methanesulphonate) varies from 10% to 30%, but in selected materials the rate for colistin may be as high as 43 to 48 % and that for polymyxin B as high as 55%. Accordingly, individual variation is high (Vaara, M. 2013, New derivatives of polymyxins, Journal of Antimicrobial Chemotherapy 2013, 68: 1213-9). The situation is made even more unfortunate by contemporary data indicating that in critically ill patients the current dosage regimens are suboptimal and lead to too low serum concentrations. Clinicians are thus advised to use larger doses, but this further increases nephrotoxicity.

Summary

It is thus an object of the present disclosure to provide a polymyxin derivative effective against Gram-negative bacteria and having reduced nephrotoxicity. The objects of the disclosure are achieved by a polymyxin derivative and pharmaceutically acceptable salts thereof and by uses thereof which are characterized by what is stated in the independent claims.

In one aspect, there is provided a compound of the general formula (I),



wherein
R1 is Dab
R2 is Thr
R3 is DThr
R4 is Dab
R5 is Dab

R6 is DPhe
R7 is Leu
R8 is Abu
R9 is Dab;
R10 is Thr; and
R(FA) is octanoyl;
or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a pharmaceutical composition comprising an effective amount of a compound or a pharmaceutically acceptable salt thereof as disclosed herein and at least one pharmaceutically acceptable carrier and/or excipient.

In yet another aspect, there is provided a compound as disclosed herein, or a pharmaceutical composition as disclosed herein, for use as a medicament.

In a further aspect, there is provided a compound as disclosed herein, or a pharmaceutical composition as disclosed herein, for use in treatment of a bacterial infection.

In yet a further aspect, there is provided a use of a compound as disclosed herein, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treatment of a bacterial infection.

The preferred embodiments of the disclosure are disclosed in the dependent claims.

Brief description of the drawings

In the following the invention will be described in greater detail by means of preferred embodiments with reference to the attached [accompanying] drawings, in which

Figure 1 shows S-BUN (mg/dL) before (day -7/-8) and during (days 2-8) treatment with polymyxin B (PMB), NAB739, or NAB815 (3 animals per group, IV, TID);

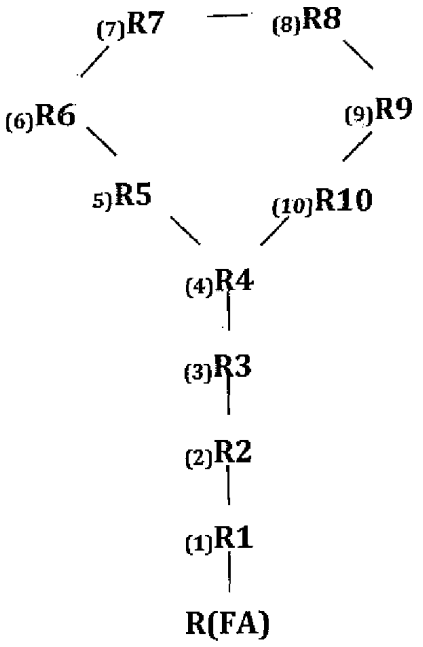
Figure 2 shows S-Crea (mg/dL) before (day -7/-8) and during (days 2-8) treatment with polymyxin B (PMB), NAB739, or NAB815 (3 animals per group, IV, TID);

Figure 3 shows U-NAG (U/L) / U-Crea (mg/dL) ratio x 10 before (day -7/-8) and during (days 2-8) treatment with polymyxin B (PMB), NAB739, or NAB815 (3 animals per group, IV, TID);

Figure 4 shows U-GGT (U/L) / U-Crea (mg/dL) ratio before (day -7/-8) and during (days 2-8) treatment with polymyxin B (PMB), NAB739, or NAB815 (3 animals per group, IV, TID).

Claims

1. A compound of the general formula (I),



wherein

R1 is Dab

R2 is Thr

R3 is DThr

R4 is Dab

R5 is Dab

R6 is DPhe

R7 is Leu

R8 is Abu

R9 is Dab;

R10 is Thr; and

R(FA) is octanoyl;

or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising an effective amount of a compound or a pharmaceutically acceptable salt thereof as claimed in claim 1 and at least one pharmaceutically acceptable carrier and/or excipient.

3. A pharmaceutical composition as claimed in claim 2, further comprising one or more other active ingredient(s).

4. A pharmaceutical composition as claimed in claim 3, wherein said other active ingredient is an antibacterial agent selected from the group consisting of clarithromycin, azithromycin, erythromycin and other macrolides, ketolides, fluoroketolides, clindamycin and other lincosamines, streptogramins, rifampin, rifabutin, rifalazil and other rifamycins, fusidic acid, mupirocin, oxazolidinones, vancomycin, dalbavancin, telavancin, oritavancin and other glycopeptide antibiotics, fluoroquinolones, bacitracin, tetracycline and fluorocycline derivatives, betalactam antibiotics, novobiocin, pleuromutilins, folate synthesis inhibitors, deformylase inhibitors, and bacterial efflux pump inhibitors.

5. A pharmaceutical composition as claimed in claim 4, wherein said antibacterial agent is selected from the group consisting of: clarithromycin, azithromycin, erythromycin, telithromycin, solithromycin, clindamycin, the streptogramin combination quinupristin-dalfopristin, eravacycline, minocycline, omadacycline, rifampin, rifabutin, rifalazil, fusidic acid, mupirocin, the oxazolidinones tedizolid and linezolid, vancomycin, dalbavancin, oritavancin, telavancin, the fluoroquinolones moxifloxacin, delafloxacin and avarafloxacin, and the folate synthesis inhibitor trimetoprim.

6. A compound as claimed in claim 1, or a pharmaceutical composition as claimed in any one of claims 2 to 5, for use as a medicament.

7. A compound as claimed in claim 1, or a pharmaceutical composition as claimed in any one of claims 2 to 5, for use in treatment of a bacterial infection.

8. A compound as claimed in claim 1, or a pharmaceutical composition as claimed in any one of claims 2 to 5, for use as claimed in claim 7, wherein the bacteria is a Gram negative bacterium.

9. A compound as claimed in claim 1, or a pharmaceutical composition as claimed in any one of claims 2 to 5, for use as claimed in claim 7, wherein said bacteria are selected from the group consisting of: *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Enterobacter cloacae*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*.

10. Use of a compound as claimed in claim 1, or a pharmaceutical composition as claimed in any one of claims 2 to 5, in the manufacture of a medicament for treatment of a bacterial infection.

11. The use as claimed in claim 10, wherein the bacteria is a Gram negative bacterium.

12. The use as claimed in claim 10 or 11, wherein said bacteria are selected from the group consisting of: *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Enterobacter cloacae*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*.