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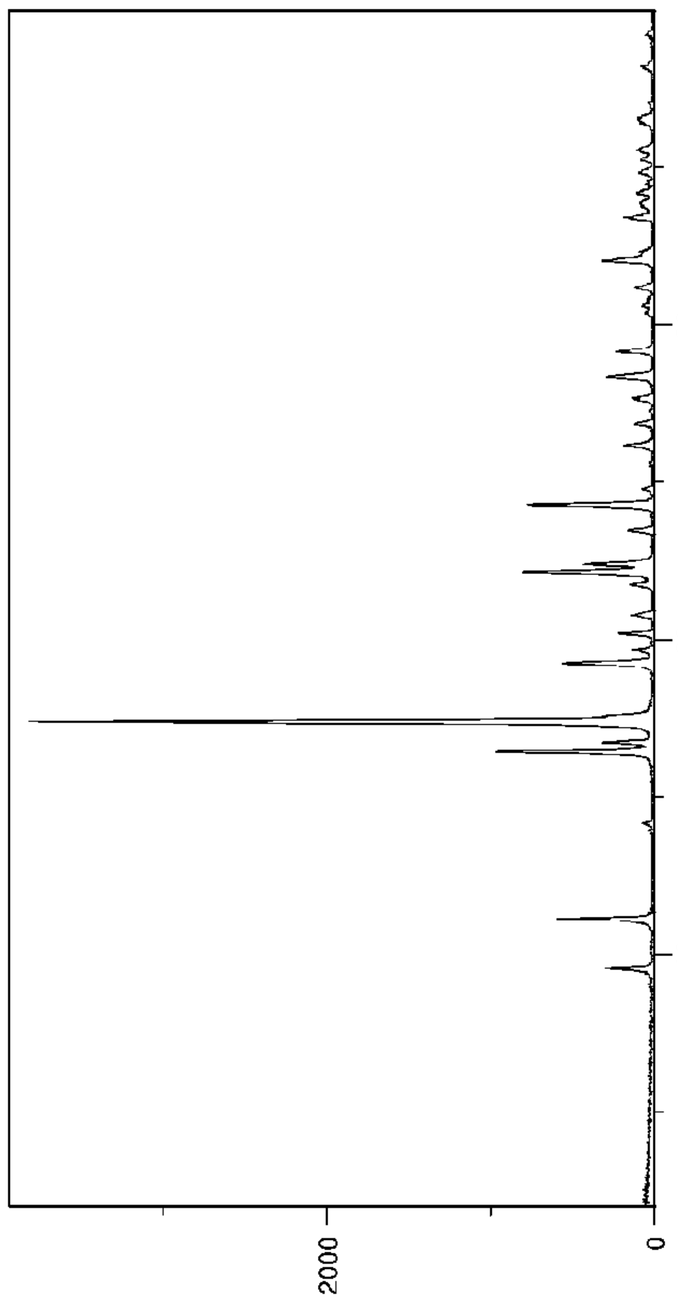
(54) Titre : ACIDE LIBRE D'AVIBACTAM
(54) Title: AVIBACTAM FREE ACID

Figure 1



(57) Abrégé/Abstract:
The present invention relates to avibactam free acid, a method for preparing avibactam free acid and a method for preparing avibactam sodium by further reacting avibactam free acid. The invention further refers to a pharmaceutical composition comprising avibactam free acid, one or more alkaline sodium salt(s) and one or more beta-lactam antibiotic(s). The pharmaceutical composition of the present invention can be used as medicament, in particular for treatment and/or prevention of bacterial infections.

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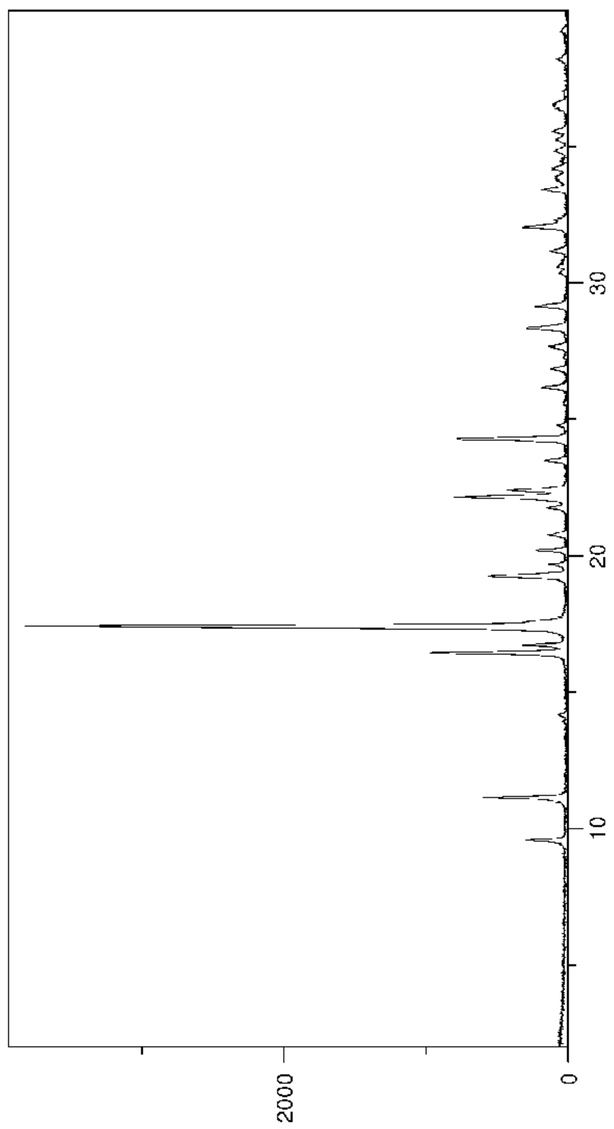
(54) Title: AVIBACTAM FREE ACID

Figure 1



(57) Abstract: The present invention relates to avibactam free acid, a method for preparing avibactam free acid and a method for preparing avibactam sodium by further reacting avibactam free acid. The invention further refers to a pharmaceutical composition comprising avibactam free acid, one or more alkaline sodium salt(s) and one or more beta-lactam antibiotic(s). The pharmaceutical composition of the present invention can be used as medicament, in particular for treatment and/or prevention of bacterial infections.

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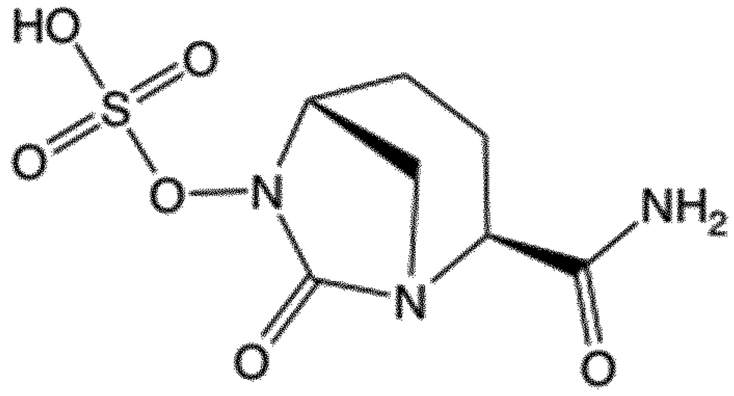
CLAIMS

1) [(2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicylco[3.2.1]octan-6-yl] hydrogen sulfate according to Formula (I)



Formula (I).

2) [(2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicylco[3.2.1]octan-6-yl] hydrogen sulfate of claim 1 being present in crystalline form.

3) A crystalline form of [(2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicylco[3.2.1]octan-6-yl] hydrogen sulfate according to claim 2 characterized by

(i) having a powder X-ray diffractogram comprising reflections at 2-Theta angles of (9.6 ± 0.2)°, (11.1 ± 0.2)° and (17.4 ± 0.2)°, when measured with CuKalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm; and/or

(ii) having a Fourier transform infrared spectrum comprising peaks at wavenumbers of (3391 ± 2) cm^{-1}, (1820 ± 2) cm^{-1} and (1688 ± 2) cm^{-1}, when measured with a diamond ATR cell.

4) A crystalline form of [(2S,5R)-2-carbamoyl-7-oxo-1,6-diazabicylco[3.2.1]octan-6-yl] hydrogen sulfate according to claim 2 characterized by

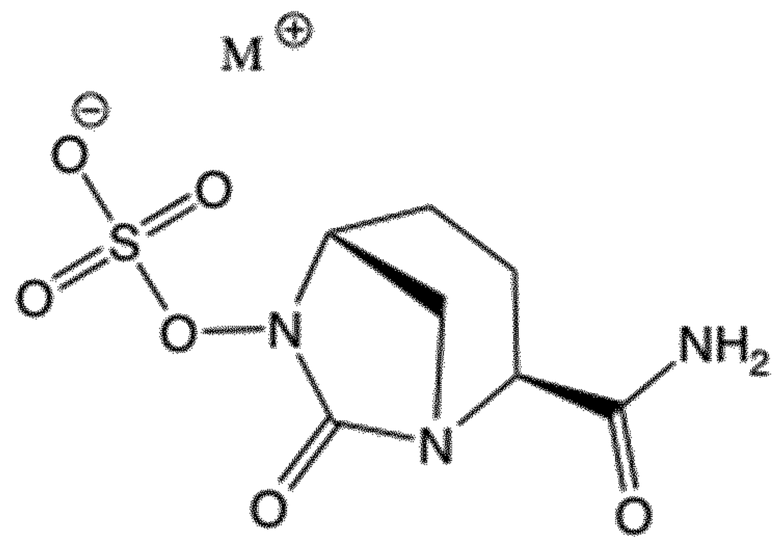
(i) having a powder X-ray diffractogram comprising reflections at 2-Theta angles of (9.3 ± 0.2)°, (10.1 ± 0.2)° and (16.7 ± 0.2)°, when measured with CuKalpha$_{1,2}$ radiation having a wavelength of 0.15419 nm; and/or

(ii) having a Fourier transform infrared spectrum comprising peaks at wavenumbers of (3403 ± 2) cm^{-1}, (1825 ± 2) cm^{-1} and (1686 ± 2) cm^{-1}, when measured with a diamond ATR cell.

5) [(2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicylco[3.2.1]octan-6-yl] hydrogen sulfate according to Formula (I) according to any one of the preceding claims having a purity of at least 95%.

6) A method for the preparation of [(2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicylco[3.2.1]octan-6-yl] hydrogen sulfate according to Formula (I) as defined in any one of the preceding claims comprising:

(a) reacting a compound according to Formula (II)



Formula (II)

wherein $M^{\oplus}$ is $N^{\oplus}RR'R''R'''$ with R, R', R'' and R''' each being independently selected from hydrogen and an alkyl group with 1 to 6 carbon atoms,

with one or more acid(s) having a pKa < -1; and

(b) optionally isolating at least a part of the compound according to Formula (I).

7) The method according to claim 6, wherein $M^{\oplus}$ is $N^{\oplus}RR'R''R'''$ with R, R', R'' and R''' each being *n*-butyl.

8) The method according to claim 6 or 7, wherein the acid having a pKa < -1 is selected from the group consisting of hydrochloric acid, nitric acid and p-toluene sulfonic acid.

9) Use of [(2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicylco[3.2.1]octan-6-yl] hydrogen sulfate according to Formula (I) for the preparation of a pharmaceutical composition.

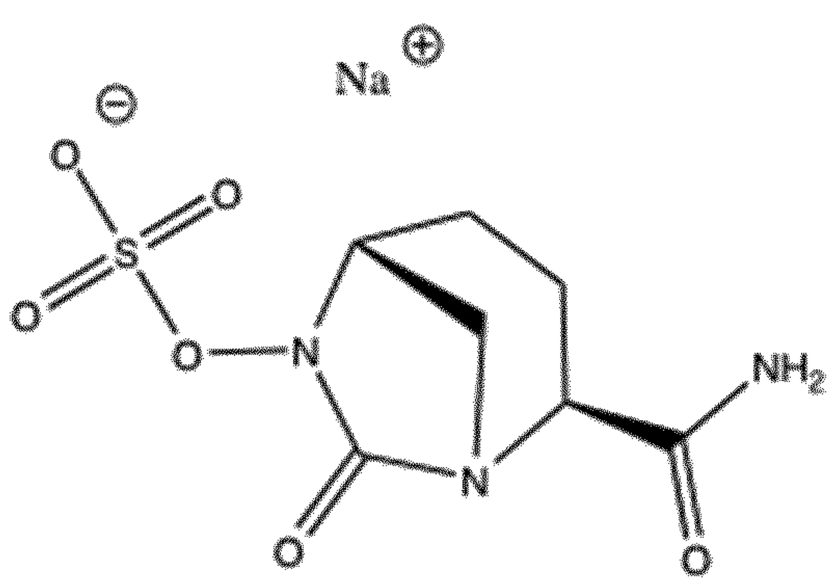
10) A pharmaceutical composition comprising an effective and/or predetermined amount of [(2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicylco[3.2.1]octan-6-yl] hydrogen sulfate according to Formula (I) as defined in any one of claims 1 to 5, one or more alkaline sodium salt(s) and one or more antibacterial agent(s), wherein at least one antibacterial agent is a beta-lactam antibiotic, preferably selected from ceftazidime and/or ceftaroline fosamil.

11) The pharmaceutical composition according to claim 10 or 11, wherein the one or more alkaline sodium salt(s) is selected from sodium carbonate and sodium hydrogen carbonate.

12) [(2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicylco[3.2.1]octan-6-yl] hydrogen sulfate according to any one of claims 1 to 5 or the pharmaceutical composition according to any one of claims 10 to 11 for use as a medicament.

13) [(2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicylco[3.2.1]octan-6-yl] hydrogen sulfate according to any one of claims 1 to 5 or the pharmaceutical composition according to any one of claims 10 to 11 for use in the treatment and/or prevention of bacterial infections.

14) A method for preparing the compound according to Formula (III)



Formula (III)

comprising

(a) reacting [(2*S*,5*R*)-2-carbamoyl-7-oxo-1,6-diazabicylco[3.2.1]octan-6-yl] hydrogen sulfate according to Formula (I) with one or more sodium salt(s) of an organic acid having 2 to 8 carbon atoms; and

(b) optionally isolating at least a part of the compound according to Formula (III).

15) The method according to claim 14, wherein the sodium salt of the organic acid having 2 to 8 carbon atoms is sodium 2-ethylhexanoate.