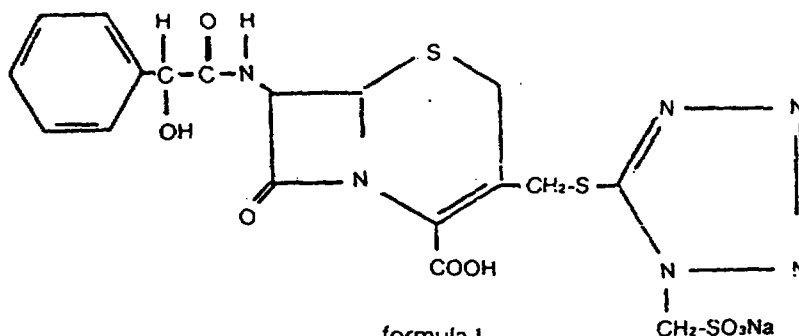


Description

This invention relates to a new cephalosporin compound, 7-D-mandelamido-3-(1-sulfomethyltetra-

razol-5-yl)-thiomethyl-3-cephem-4-carboxylic acid monosodium salt, and hydrates and solvates thereof, which is represented by the following structural formula:

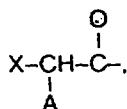


formula I

The compound of formula I has unique antibacterial activity when administered parenterally. The invention also comprises pharmaceutical compositions for treating bacterial infections containing the compound of formula I.

The compound of formula I is also known as SK&F 75073-Z, cefonicid monosodium salt and "Monocid" monosodium salt. A New Drug Application for cefonicid disodium salt ($-\text{COONa}$ at the 4-position) is currently pending before the United States Food and Drug Administration.

The compound of formula I is included within the large generic class of compounds disclosed and claimed in U.S. Patent No. 4 048 311. Specifically, see formula I (column 1, lines 21-58) where R^1 is hydrogen, n is one, R^2 is hydroxy, R^3 is



X is phenyl and A is OH. These compounds are described as existing in either the free acid form or as a "non-toxic pharmaceutically acceptable salt thereof" (line 58). At column 2, lines 66-67, the compound 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid is identified as an example of the invention. Example 1 (column 11, line 25 to column 12, line 6) relates to preparation of 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid, which is isolated and analyzed as its disodium salt. In addition, 7-mandelamido-3-(1-sulfomethyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid is claimed as the free acid or an unspecified "pharmaceutically acceptable" salt in claims 1, 2, 4, 6, 8, 9, 10 and 12. 7-Mandelamido-3-(1-sulfomethyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid disodium salt is claimed in claim 29. 7-D-Mandelamido-3-(1-sulfomethyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid is claimed in claim 30.

The antibacterial activity of 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid is fully described in U.S. Patent No. 4 048 311 (see column 6, line 19 to column 9, line 41 and the data for compound I in tables 1 and 2). Of particular note are the exceptionally and advanta-

geously high blood serum levels and half lives achieved, which permit administration of the antibacterial agent on a one dose per day basis.

It has now unexpectedly been found that the newly prepared monosodium salt of 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid is a highly stable form of the antibiotic, while retaining advantageous antibacterial activity. As compared to the disodium salt, the monosodium salt exhibits a significantly higher degree and longer duration of stability at elevated temperatures. Thus, the antibiotic in its monosodium salt form can be stored for prolonged periods of time without the need for refrigeration or special handling. Due to this enhanced stability, the compound of formula I is advantageous from a commercial viewpoint.

Comparative physical and chemical stability data for 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid disodium salt and monosodium salt appears in table 1, below. Stability data for 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid monosodium salt at various temperatures and for various periods of time appears in table 2, below. Lyophilized vials, 10 ml capacity, each containing 0.5 gm of the cephalosporin were used in the stability studies; reconstitution was achieved with 2.0 ml of sterile water.

Table 1

"Comparative stability between 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid mono- and disodium salts at 50 °C"

Time (weeks)	Purity assay	Total organic material impurities	Water content	Clarity upon reconstitution
Monosodium salt (formula I):				
0	94.4%	3.1%	2.1%	clear
1	92.3%	3.3%	2.2%	clear
2	90.2%	3.2%	1.9%	clear
3	90.1%	3.1%	2.0%	clear

Time (weeks)	Purity assay	Total organic material impurities	Water content	Clarity upon reconstitution
4	92.6%	3.2%	1.5%	clear
5	91.7%	3.2%	1.5%	clear
6	89.5%	3.4%	2.7%	clear
7	86.9%	3.7%	1.7%	clear
8	92.6%	3.6%	1.4%	clear
9	91.1%	3.7%	1.6%	clear
10	91.1%	4.0%	1.3%	clear
Disodium salt				
0	93.3%	3.1%	2.3%	clear
1	91.4%	5.8%	2.9%	cloudy (after 3 days)
2	89.5%	7.2%	2.4%	cloudy
3	86.7%	7.2%	2.0%	cloudy
4	90.0%	7.9%	2.3%	cloudy
5	85.6%	8.3%	2.1%	cloudy
6	96.2%	8.5%	3.1%	cloudy
7	81.1%	8.9%	1.7%	cloudy
8	82.9%	9.8%	2.0%	cloudy
9	83.5%	10.2%	2.1%	cloudy
10	83.4%	10.4%	1.9%	cloudy

Table 2

Stability of 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid monosodium salt at various temperatures and times

Time (weeks)	Temperature	Dry appearance	pH	Impurities	Water content
0	-	white	2.1	3.0%	0.8%
1	50 C	white	2.1	-	1.8%
1	60 C	white	2.2	3.5%	1.4%
1	85 C	yellow	2.2	-	1.3%
2	50 C	white	2.2	3.4%	2.0%
2	60 C	white	2.2	4.0%	1.7%
4	40 C	white	2.2	2.7%	1.7%
4	50 C	white	2.2	3.4%	1.7%
5	40 C	-	2.4	-	0.5%
6	50 C	-	-	-	1.4%
12	ambient	-	2.3	3.4%	1.4%
12	40 C	-	2.3	3.6%	1.4%
24	ambient	-	2.3	4.1%	3.2%

*tetrazole and other cephalosporin materials

From an analysis of the data presented in table 1 it is apparent that 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid monosodium salt resists decomposition and clouding upon reconstitution to a significantly greater degree than the disodium salt. For example, after ten weeks at 50 C the monosodium salt is still

approximately the same purity as the disodium salt after only a few days (less than one week). In addition, as evidenced by the data presented in table 2, 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid monosodium salt remains stable up to six (6) months at ambient temperatures.

The compound of formula 1 is prepared by treating an aqueous solution of 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid disodium salt with an acidic cation exchange resin or with an acid of greater strength than the 4-carboxylic acid function of the starting material. When an acidic cation exchange resin is employed, a slurry is preferably used if the resin is a strongly acidic one, while a column is preferably used if the resin is a weakly acidic one. Sulfonated polystyrene resins, such as Amberlite[®] Ir-120(H), are preferred. When an acid is used to effect the conversion, hydrochloric acid, sulfuric acid or trifluoroacetic acid is preferred.

Alternatively, the compound of formula 1 is prepared by titration of 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid with a stoichiometric amount of a suitable sodium-containing base such as sodium carbonate, sodium bicarbonate or sodium hydroxide.

Yet another way in which the compound of formula 1 can be prepared is by treatment of a 7-D-(OH-protected mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid monosodium salt (-COOH at position 4) such as, for example, 7-(O α -formyloxyphenylacetamidol)-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid monosodium salt with a dilute acid such as, for example, dilute hydrochloric acid.

The compound of formula 1 may exist in a hydrated or solvated form. Any and all such hydrates and solvates are included with the scope of this invention.

Pharmaceutical compositions having antibacterial activity which comprise a pharmaceutical carrier containing an active but nontoxic quantity of the compound of formula 1 are also objects of this invention. The administration may be by parenteral injection such as subcutaneously, intramuscularly or intravenously. The injection of suitable prepared sterile solutions or suspensions containing an effective nontoxic amount of the compound of formula 1 is the preferred route of administration. Aqueous-based pharmaceutical compositions are preferred.

The compound of formula 1 is formulated and administered in the same manner as other injectable cephalosporins. The dosage regimen comprises administration, preferably by injection, of an active but nontoxic quantity of the compound of formula 1 selected from the dosage unit range of from 100 to 1,000 mg with the total daily dosage regimen being from 400 mg to 6 g. The anticipated adult daily dosage regimen will be about from 500 mg to about 2 g, preferably about 1 g. The precise dosages are dependent upon the age and weight of the subject and on the infection being treated and can be determined by those skilled in the art.



Example 1

Preparation of 7-D-mandelamido-3-(1-sulfomethyl-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid monosodium salt.

7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)-thiomethyl-3-cephem-4-carboxylic acid disodium salt (1.0 g) was dissolved in 20 ml of sterile water. The solution was adjusted to pH 2.0 by addition of Amberlite® IR-120H resin (less than 1.0 ml), which had been pre-washed with sterile water. The resin was filtered off and the filtrate was lyophilized overnight to give the title compound.



Calculated	Found
38.27% C	37.33% C
3.04% H	3.26% H
14.89% N	14.84% N
22.68% O	23.99% O
17.04% S	16.79% S
4.07% Na	3.97% Na

Example 2

Preparation of a pharmaceutical composition comprising 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid monosodium salt.

An injectable pharmaceutical composition is formed by adding sterile water or sterile saline solution (ca. 2 ml) to 1 g of 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid monosodium salt.

Claims

For the contracting states BE, CH, DE, FR, GB, IT, LI, LU, NL and SE

1. 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid monosodium salt or a hydrate or solvate thereof.
2. 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid monosodium salt.
3. A compound according to either claim 1 or 2 for use as a therapeutic agent.
4. A compound according to either claim 1 or 2 for use as an antibacterial agent.
5. A compound according to any one of claims 1 to 4 in lyophilized form suitable for reconstitution in an aqueous medium.
6. A pharmaceutical composition comprising a compound according to any one of claims 1 to 5 and a pharmaceutically acceptable carrier.
7. A composition according to claim 6 in aqueous form.
8. A composition according to claim 7 in sterile form.
9. A composition according to either claim 7 or 8 comprising from 100 mg to 1,000 mg of a compound according to either claim 1 or claim 2.

10. A composition according to claim 9 comprising 1,000 mg of a compound according to either claim 1 or claim 2.

11. A reconstituted aqueous antibacterial composition comprising a compound according to either claim 1 or claim 2.

12. A process for preparing 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid monosodium salt, or a solvate or hydrate thereof, which comprises:

(a) treating an aqueous solution of 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid disodium salt with an acidic cation exchange resin; or

(b) treating an aqueous solution of 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid disodium salt with an acid of greater strength than the 4-carboxylic acid function of the starting material; or

(c) titrating 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid with a stoichiometric amount of a suitable sodium-containing base; or

(d) treating 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid monosodium salt, wherein the hydroxyl group on the 7-position side chain is suitably protected and the 4-position carboxylic acid function is a free acid, with a dilute acid.

13. The process of claim 12 further comprising lyophilizing the 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid monosodium salt, or solvate or hydrate thereof, thus formed.

14. A process for preparing a pharmaceutical composition which comprises bringing into association a compound according to either claim 1 or 2 and a pharmaceutically acceptable carrier.

Claims

for the contracting state Austria

1. A process for preparing 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid monosodium salt, or a solvate or hydrate thereof, which comprises:

(a) treating an aqueous solution of 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid disodium salt with an acidic cation exchange resin; or

(b) treating an aqueous solution of 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid disodium salt with an acid of greater strength than the 4-carboxylic acid function of the starting material; or

(c) titrating 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid with a stoichiometric amount of a suitable sodium-containing base; or

(d) treating 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid monosodium salt, wherein the hydroxyl group on the 7-position side chain is suitably protected and the



position carboxylic acid function is a free acid, with a dilute acid.

2. The process of claim 1 further comprising lyophilizing the 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid monosodium salt, or solvate or hydrate thereof, thus formed.

3. A process for preparing a pharmaceutical composition which comprises bringing 7-D-mandelamido-3-(1-sulfomethyltetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic acid monosodium salt, or a hydrate or solvate thereof, and a pharmaceutically acceptable carrier therefor into association.

4. The process of claim 3 wherein the pharmaceutical composition is an antibacterial composition.

5. The process of claim 4 wherein the carrier is water.

Patentansprüche

für die Vertragsstaaten BE, CH, DE, FR, GB, IT, LI, LU, NL und SE

1. 7-D-Mandelamido-3-(1-sulfomethyltetrazol-5-yl)-thiomethyl-3-cephem-4-carbonsäure-Mononatriumsalz oder dessen Hydrat oder Solvat.

2. 7-D-Mandelamido-3-(1-sulfomethyltetrazol-5-yl)-thiomethyl-3-cephem-4-carbonsäure-Mononatriumsalz.

3. Verbindung nach Anspruch 1 oder 2 zur Anwendung als Arzneimittel.

4. Verbindung nach Anspruch 1 oder 2 zur Anwendung als antibakterielles Mittel.

5. Verbindung nach einem der Ansprüche 1 bis 4 in gefriergetrockneter Form, geeignet zur Rekonstitutionierung in einem wäßrigen Medium.

6. Arzneimittel, enthaltend eine Verbindung nach einem der Ansprüche 1 bis 5 und einem pharmazeutisch verträglichen Träger.

7. Mittel nach Anspruch 6 in wäßriger Form.

8. Mittel nach Anspruch 7 in steriler Form.

9. Mittel nach Anspruch 7 oder 8, enthaltend 100 bis 1000 mg einer Verbindung nach Anspruch 1 oder Anspruch 2.

10. Mittel nach Anspruch 9, enthaltend 1000 mg einer Verbindung nach Anspruch 1 oder Anspruch 2.

11. Rekonstituierte wäßrige antibakterielle Zusammensetzung, enthaltend eine Verbindung nach Anspruch 1 oder Anspruch 2.

12. Verfahren zur Herstellung von 7-D-Mandelamido-3-(1-sulfomethyltetrazol-5-yl)-thiomethyl-3-cephem-4-carbonsäure-Mononatriumsalz oder dessen Solvat oder Hydrat, dadurch gekennzeichnet, daß man

(a) eine wäßrige Lösung von 7-D-Mandelamido-3-(1-sulfomethyltetrazol-5-yl)-thiomethyl-3-cephem-4-carbonsäure-Dinatriumsalz mit einem sauren Kationenaustauscherharz behandelt, oder

(b) eine wäßrige Lösung von 7-D-Mandelamido-3-(1-sulfomethyltetrazol-5-yl)-thiomethyl-3-cephem-4-carbonsäure-Dinatriumsalz mit einer Säure, die stärker ist als die Carbonsäure-Funktion in der 4-Stellung der Ausgangsverbindung, umsetzt, oder

(c) 7-D-Mandelamido-3-(1-sulfomethyltetrazol-5-yl)-thiomethyl-3-cephem-4-carbonsäure mit einer stöchiometrischen Menge einer geeigneten Natriumionen enthaltenden Base titriert oder

(d) 7-D-Mandelamido-3-(1-sulfomethyltetrazol-5-yl)-thiomethyl-3-cephem-4-carbonsäure-Mononatriumsalz, bei dem die Hydroxylgruppe in der 7-Stellung der Seitenkette in geeigneter Weise geschützt ist und die Carbonsäure-Funktion in der 4-Stellung als freie Säure vorliegt, mit einer verdünnten Säure umsetzt.

13. Verfahren nach Anspruch 12, dadurch gekennzeichnet, daß man das erhaltene 7-D-Mandelamido-3-(1-sulfomethyltetrazol-5-yl)-thiomethyl-3-cephem-4-carbonsäure-Mononatriumsalz oder dessen Solvat oder Hydrat gefriertrocknet.

14. Verfahren zur Herstellung eines Arzneimittels, dadurch gekennzeichnet, daß man eine Verbindung nach Anspruch 1 oder 2 mit einem pharmazeutisch verträglichen Träger in Verbindung bringt.

Patentansprüche

für den Vertragsstaat AT

1. Verfahren zur Herstellung von 7-D-Mandelamido-3-(1-sulfomethyltetrazol-5-yl)-thiomethyl-3-cephem-4-carbonsäure-Mononatriumsalz oder dessen Solvat oder Hydrat, dadurch gekennzeichnet, daß man entweder

(a) eine wäßrige Lösung von 7-D-Mandelamido-3-(1-sulfomethyltetrazol-5-yl)-thiomethyl-3-cephem-4-carbonsäure-Dinatriumsalz mit einem sauren Kationenaustauscherharz behandelt, oder

(b) eine wäßrige Lösung von 7-D-Mandelamido-3-(1-sulfomethyltetrazol-5-yl)-thiomethyl-3-cephem-4-carbonsäure-Dinatriumsalz mit einer Säure, die stärker ist als die Carbonsäure-Funktion in der 4-Stellung, der Ausgangsverbindung, umsetzt, oder

(c) 7-D-Mandelamido-3-(1-sulfomethyltetrazol-5-yl)-thiomethyl-3-cephem-4-carbonsäure mit einer stöchiometrischen Menge einer geeigneten Natriumionen enthaltenden Base titriert, oder

(d) 7-D-Mandelamido-3-(1-sulfomethyltetrazol-5-yl)-thiomethyl-3-cephem-4-carbonsäure-Mononatriumsalz, bei dem die Hydroxylgruppe in der 7-Stellung der Seitenkette in geeigneter Weise geschützt ist und die Carbonsäure-Funktion in der 4-Stellung als freie Säure vorliegt, mit einer verdünnten Säure umsetzt.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß man das erhaltene 7-D-Mandelamido-3-(1-sulfomethyltetrazol-5-yl)-thiomethyl-3-cephem-4-carbonsäure-Mononatriumsalz oder dessen Solvat oder Hydrat gefriertrocknet.

3. Verfahren zur Herstellung eines Arzneimittels, dadurch gekennzeichnet, daß man 7-D-Mandelamido-3-(1-sulfomethyltetrazol-5-yl)-thiomethyl-3-cephem-4-carbonsäure-Mononatriumsalz oder dessen Hydrat oder Solvat mit einem pharmazeutisch verträglichen Träger in Verbindung bringt.



4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß das Arzneimittel ein antibakterielles Mittel ist.

5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß der Träger Wasser ist.

Revendications

pour les Etats Contractants BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Le sel monosodique d'acide 7-D-mandelamido-3-(1-sulfométhyltétrazol-5-yl)-thiométhyl-3-cephem-4-carboxylique ou un hydrate ou solvate du même.

2. Le sel monosodique d'acide 7-D-mandelamido-3-(1-sulfométhyltétrazol-5-yl)-thiométhyl-3-cephem-4-carboxylique.

3. Un composé selon la revendication 1 ou 2 à employer en tant qu'agent thérapeutique.

4. Un composé selon la revendication 1 ou 2 à employer en tant qu'agent antibactérien.

5. Un composé selon n'importe laquelle des revendications de 1 à 4 sous forme lyophilisée convenant à la reconstitution en un milieu aqueux.

6. Une composition pharmaceutique comprenant un composé selon n'importe laquelle des revendications de 1 à 5 et un support pharmaceutiquement acceptable.

7. Une composition selon la revendication 6 sous forme aqueuse.

8. Une composition selon la revendication 7 sous forme stérile.

9. Une composition selon la revendication 7 ou 8 comprenant de 100 mg à 1000 mg d'un composé selon la revendication 1 ou 2.

10. Une composition selon la revendication 9 comprenant 1000 mg d'un composé selon la revendication 1 ou 2.

11. Une composition antibactérienne aqueuse reconstituée comprenant un composé selon la revendication 1 ou 2.

12. Un procédé pour la préparation d'un sel monosodique d'acide 7-D-mandelamido-3-(1-sulfométhyltétrazol-5-yl)-thiométhyl-3-cephem-4-carboxylique, ou un solvate ou hydrate du même, qui comprend:

(a) le traitement d'une solution aqueuse du sel disodique d'acide 7-D-mandelamido-3-(1-sulfométhyltétrazol-5-yl)-thiométhyl-3-cephem-4-carboxylique avec une résine d'échange de cations acide; ou

(b) le traitement d'une solution aqueuse du sel disodique d'acide 7-D-mandelamido-3-(1-sulfométhyltétrazol-5-yl)-thiométhyl-3-cephem-4-carboxylique avec un acide d'une force supérieure à la fonction acide 4-carboxylique de la matière de départ; ou

(c) le titrage de l'acide 7-D-mandelamido-3-(1-sulfométhyltétrazol-5-yl)-thiométhyl-3-cephem-4-carboxylique avec une quantité stoechiométrique d'une base convenable contenant du sodium; ou

(d) le traitement du sel monosodique d'acide 7-D-mandelamido-3-(1-sulfométhyltétrazol-5-yl)-thio-

méthyl-3-cephem-4-carboxylique, dans lequel le groupe hydroxyl de la chaîne latérale à la position 7 est convenablement protégé et la fonction d'acide carboxylique à la position 4 est un acide libre, avec un acide dilué.

13. Le procédé de la revendication 12 comprend encore la lyophilisation du sel monosodique de l'acide 7-D-mandelamido-3-(1-sulfométhyltétrazol-5-yl)-thiométhyl-3-cephem-4-carboxylique, ou le solvate ou l'hydrate du même ainsi formé.

14. Un procédé pour la préparation d'une composition pharmaceutique qui comprend la mise en association d'un composé selon l'une ou l'autre des revendications 1 ou 2 et un support pharmaceutiquement acceptable.

Revendications

pour l'Etat Contractant AT

1. Un procédé pour la préparation d'un sel monosodique d'acide 7-D-mandelamido-3-(1-sulfométhyltétrazol-5-yl)-thiométhyl-3-cephem-4-carboxylique, ou un solvate ou hydrate du même, qui comprend:

(a) le traitement d'une solution aqueuse du sel disodique d'acide 7-D-mandelamido-3-(1-sulfométhyltétrazol-5-yl)-thiométhyl-3-cephem-4-carboxylique avec une résine d'échange de cations acide; ou

(b) le traitement d'une solution aqueuse du sel disodique d'acide 7-D-mandelamido-3-(1-sulfométhyltétrazol-5-yl)-thiométhyl-3-cephem-4-carboxylique avec un acide d'une force supérieure à la fonction acide 4-carboxylique de la matière de départ; ou

(c) le titrage de l'acide 7-D-mandelamido-3-(1-sulfométhyltétrazol-5-yl)-thiométhyl-3-cephem-4-carboxylique avec une quantité stoechiométrique d'une base convenable contenant du sodium; ou

(d) le traitement du sel monosodique d'acide 7-D-mandelamido-3-(1-sulfométhyltétrazol-5-yl)-thiométhyl-3-cephem-4-carboxylique, dans lequel le groupe hydroxyl de la chaîne latérale à la position 7 est convenablement protégé et la fonction d'acide carboxylique à la position 4 est un acide libre, avec un acide dilué.

2. Le procédé de la revendication 1 comprend encore la lyophilisation du sel monosodique de l'acide 7-D-mandelamido-3-(1-sulfométhyltétrazol-5-yl)-thiométhyl-3-cephem-4-carboxylique, ou le solvate ou l'hydrate du même ainsi formé.

3. Un procédé pour la préparation d'une composition pharmaceutique qui comprend la mise en association d'un sel monosodique d'acide 7-D-mandelamido-3-(1-sulfométhyltétrazol-5-yl)-thiométhyl-3-cephem-4-carboxylique, ou un hydrate ou solvate du même avec un support du même pharmaceutiquement acceptable.

4. Le procédé de la revendication 3 dans lequel la composition pharmaceutique est une composition antibactérienne.

5. Le procédé de la revendication 4 dans lequel le support est de l'eau.