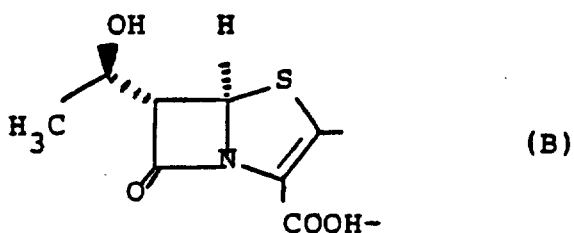


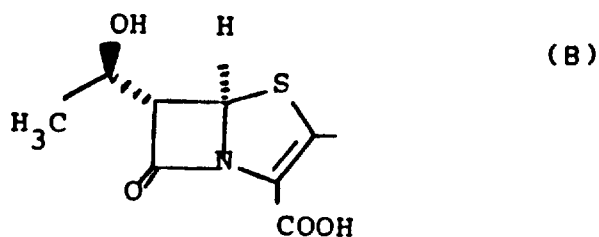
Abstract of the disclosure

A pharmaceutical formulation having a synergistic anti-bacterial activity and comprising

- a) a cephalosporin derivative or a physiologically acceptable salt or ester thereof and
- b) a penem antibiotic of the basic structure (B)

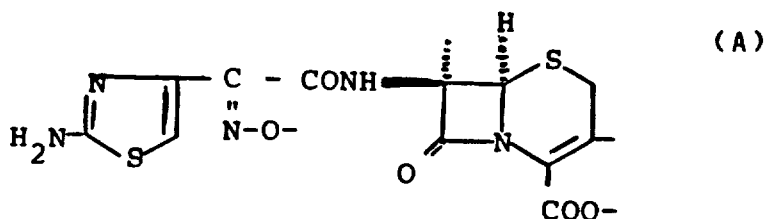


or a physiologically acceptable salt or ester thereof, a process for preparing such a formulation and its use for the treatment of bacterial infections.



or physiologically acceptable salts or esters thereof.

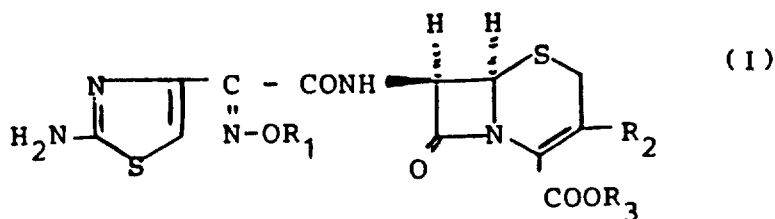
Amongst the cephalosporin derivatives, aminothiazole-
cephalosporins and physiologically acceptable salts or
esters thereof are preferred according to the invention,
in particular those having the basic structure (A)



in which the =N-O- group is in the syn-position, such as
are described, for example, in German Offenlegungsschriften
No. 2,702,501, 2,713,272, 2,715,385, 2,810,922, 2,921,316
and 2,922,036, in EP-A 0,064,740, in U.S. Patents
4,278,793 and 4,501,739 and in GB-A 2,105,334 and
2,105,335. However, other cephalosporins such as, for
example, N-acyl-phenylglycine-cephalosporins or those in
which the group -CH₂- takes the place of the -C(=N-O)-
group in the basic structure (A) can also be used accord-
ing to the invention.

Penem antibiotics of the basic structure (B) are de-
scribed, for example, in EP-A 0,069,377, EP-A 0,170,028,
GB-A 85.20,631, EP-A 121,502, British Patent 2,097,786
and Belgian Patent 898,603.

Of the cephalosporin antibiotics of the basic structure
(A), those of the general formula I are particularly pre-
ferred

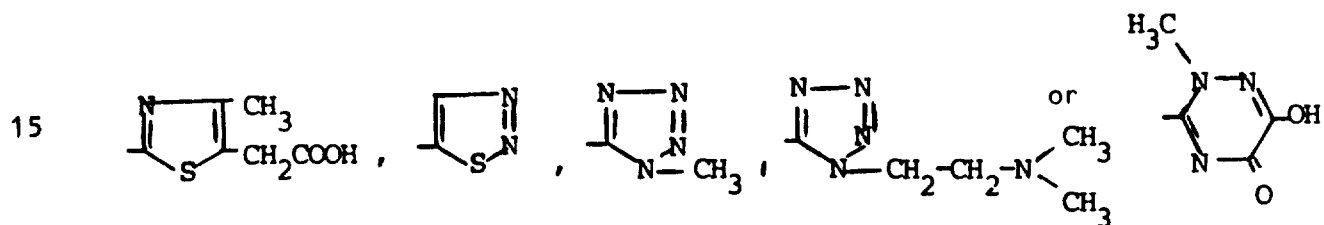


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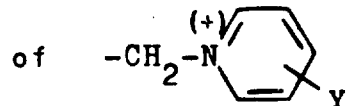
in which

R₁ can be hydrogen, C₁-C₄-alkyl or carboxy-C₁-C₄-alkyl and the group =N-OR₁ is in the syn-position,

R₂ can have the meaning of hydrogen, methyl, methoxy, vinyl, acetoxymethyl or carbamoyloxymethyl, of -CH₂S-X, with X =



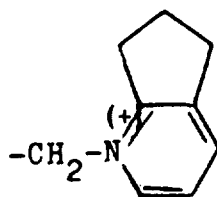
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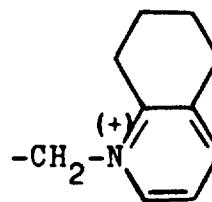
with Y = hydrogen, C₁-C₄-alkylthio, C₁-C₄-alkoxy or C₃-C₅-cycloalkyl,

25

of



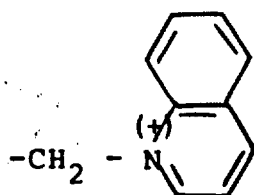
or



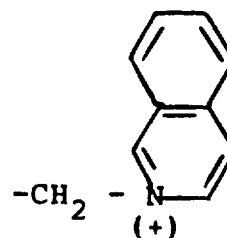
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it being possible for the fused rings also to be in the 3,4-position and also to be interrupted by oxygen, of

35



or



of thienopyridinio-methyl, furopyridinio-methyl or of 5-methyl-tetrazol-2-yl-methyl

and

- 5 R_3 is hydrogen, a physiologically acceptable cation, a physiologically acceptable ester radical or - if the structure $-CH_2-\overset{(+)}{V}$ appears in R_2 - can represent a negative charge.

- 10 If R_1 is C_1 - C_4 -alkyl, examples are methyl, ethyl and propyl, preferably methyl.

- 15 If R_1 is carboxy- C_1 - C_4 -alkyl, carboxymethyl, carboxy-ethyl, carboxypropyl, preferably the radical $-CH_2-COOH$, but especially the radical

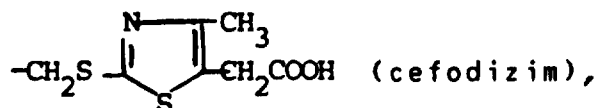


- 20 Amongst the substituted pyridinium-methyl radicals listed above, 2,3-cyclopenteno- and 2,3-cyclohexeno-pyridinium-methyl and 4-methylthio-, 4-cyclopropyl- and 3-methoxy-pyridinium-methyl as well as 3,4-cyclopenteno- and 3,4-cyclohexeno-pyridinium-methyl are preferred.

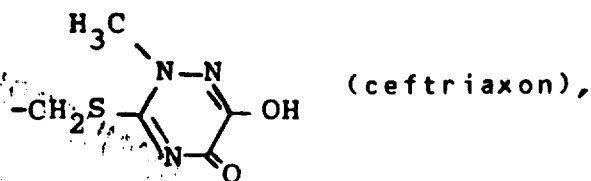
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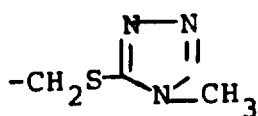
Those compounds of the formula I are of very particular interest according to the invention in which R_1 is methyl and R_2 is $-CH_2-OCOCH_3$ (cefotaxim),

30



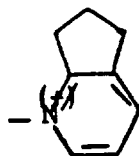
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(cefmenoxim) or

5



(cefpirom), or

10

R_1 is $-\text{CH}_2\text{COOH}$ and R_2 is $-\text{CH}=\text{CH}_2$ (cefixim), cefodizim, cefpirom, ceftriaxon and especially cefotaxim in turn being in a preferred position within this group.

15

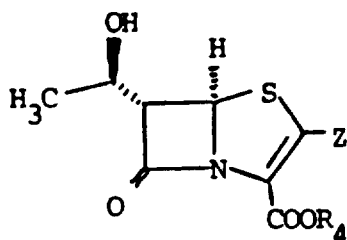
If R_2 represents a $-\text{CH}_2$ -pyridinium compound, the carboxyl group in the general formula I is present as an inner salt ($-\text{COO}^{(-)}$).

20

As cephalosporin derivatives of particular interest, cefotiam from amongst the aminothiazole-cephalosporins which contain $-\text{CH}_2-$ in place of $-\text{C}(=\text{N}-\text{OR}_1)-$ and cefoperazon from amongst the N-acyl-phenylglycine-cephalosporins should also be mentioned.

25

Of the penem antibiotics of the basic structure B, those of the general formula II are particularly preferred



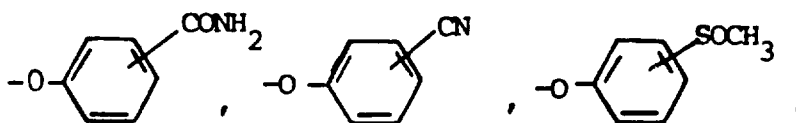
(II)

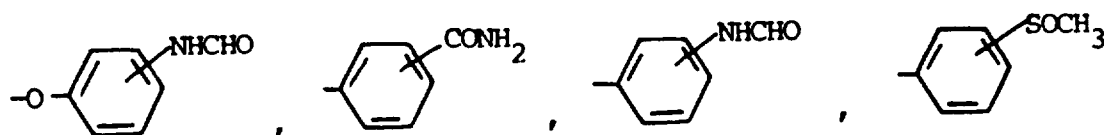
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in which

35

Z can be

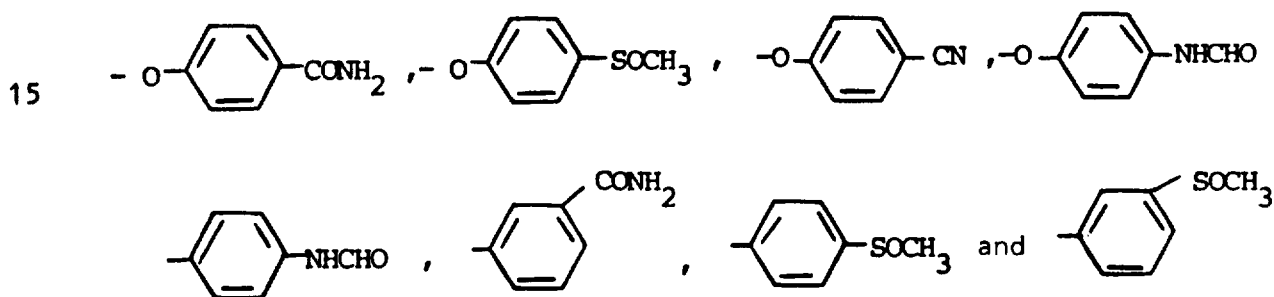




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$-\text{CH}_2-\text{O}-\text{CONH}_2$, $-\text{S}-(\text{CH}_2)_2-\text{O}-\text{CONH}_2$ or $-\text{S}-(\text{CH}_2)_3-\text{SO}_2\text{NH}_2$ and

10 R_4 is hydrogen, a physiologically acceptable cation or a physiologically acceptable ester radical. Of the substituted phenoxy and phenyl substituents listed above, the radicals



20

are preferred, and the 3-carbamoyl-phenoxy radical (HRE 664) is to be particularly singled out.

25 Accordingly, a combination of cefodizim or cefpirom, and especially of cefotaxim and the penem HRE 664, is of particular interest according to the invention.

30 R_3 and R_4 can be hydrogen or a physiologically acceptable cation such as, for example, an alkali metal cation, preferably potassium or sodium, in particular sodium, or also other physiologically acceptable salts, known from the literature, with alkaline earth metal ions or organic ammonium ions (cf., for example, U.S. Patent 4,278,793).

35 Moreover, R_3 and R_4 can be a physiologically acceptable ester radical, of interest especially for enteral administration, such as, for example, an acyloxymethyl or acyloxyethyl radical having 2 to 12, preferably 2 to 6, carbon atoms in the acyl moiety, preferably acetoxymethyl,

1'-(acetoxymethyl or pivaloyloxymethyl, 5-methyl-1,3-dioxalen-2-on-4-yl-methyl, or also other physiologically acceptable esters such as are described, for example, in EP-A 0,170,028.

5

The preparation of the components, which can be used according to the invention, in the active compound combination is described by way of example in the patent rights quoted above.

10

The combination, according to the invention, of cephalosporins and penems has a strong antibacterial action and is therefore very particularly suitable for the treatment of bacterial infections. The essential fact is that the action of the two components does not show additive behavior but that, rather, an unexpected, strong synergistic effect appears.

15

Even in the case of pathogens, towards which one individual component alone does not have a significant antibacterial action, a synergistic effect can be observed in combination.

20

The formulations according to the invention thus cover a spectrum of pathogens at low minimum inhibitory concentrations, which are not reached by the individual components.

25

For the above reasons, the formulation according to the invention is superior to the individual components in the treatment of bacterial infections. It allows to administer lower dosages of the individual components and nevertheless to achieve a greater therapeutic effect.

30

The invention also relates to a process for the preparation of such a formulation, which comprises bringing

35

a) a cephalosporin derivative or physiologically acceptable salts or esters thereof and

b) a penem antibiotic of the basic structure (B) or physiologically acceptable salts or esters thereof

5 together with (a) physiologically acceptable excipient(s) and, if appropriate, further auxiliaries or additives into a suitable administration form.

10 Moreover, the invention relates quite generally to pharmaceutical products which comprise side by side in an un-mixed form

a) a cephalosporin derivative or physiologically acceptable salts or esters thereof and
15 b) a penem antibiotic of the basic structure (B) or physiologically acceptable salts or esters thereof

as a combination product for simultaneous or separate application or for application spaced out in time in the treatment of bacterial infections.

20

The dosages of the cephalosporin derivative and of the penem antibiotic are preferably selected in the formulations according to the invention such that the individual components would not yet shown an adequate or full activity.
25 The daily dose of the combinations according to the invention (sum of the individual components) is between about 1 to 16 g, preferably about 4 to 8 g. The ratio of the individual components in the combination can be between about 1:9 and 9:1, preferably between about 1:5 and
30 5:1. The dose in one administration unit can be chosen, for example, between about 50 and 2,000 mg.

Since the preparation of the cephalosporin component in general requires less effort and is therefore also less
35 expensive than the preparation of the penem antibiotic, a combination according to the invention in which the cephalosporin proportion is higher than that of the penem will be preferable for this reason alone.

The formulations or products according to the invention can be administered parenterally or orally. Parenteral administration is preferred.

5 The active compound combinations according to the invention, which can be used in chemotherapy, can be used for the preparation of pharmaceutical products which contain an effective amount of the active substances together with excipients and which are suitable for enteral and parenteral administration. Injectable solutions are preferably isotonic aqueous solutions or suspensions, which may have been sterilized and can contain auxiliaries such as preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating the osmotic pressure and/or buffer substances. The pharmaceutical products according to the invention which, if desired, can contain further chemotherapeutically valuable substances, are prepared, for example, by means of conventional processes.

20 For parenteral administration, the combination according to the invention is preferably dissolved, immediately before use, in sterile water or - if necessary - a buffer solution such as, for example, a phosphate or carbonate buffer such as is conventionally used for these purposes, and subsequently administered.

The examples which follow serve to explain the invention without restricting the latter thereto.

30

Example 1

Action of the combination of the sodium salt of 5R,6S-6-(1R-hydroxyethyl)-3-(4-carbamoylphenoxy)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-carboxylic acid (HRE 664, marked (1) in the Table) and of the sodium salt of cefotaxim (2) towards Gram-positive and Gram-negative test strains. To determine the synergism, mixtures of compound (1) with compound (2) were prepared in a ratio of 1:1,

1:2 and 1:3. The MIC values were tested by comparison with the individual substances.

Table 1

		<u>MIC in mg/l</u>				
		(1)	(2)	(1) : (2)		
	<u>Pathogen</u>	<u>alone</u>	<u>alone</u>	1:1	1:2	1:3
5	Staph. SG 511	0,062	2	0.125	0.125	0.125
	Staph. 285	0.062	2	0.125	0.125	0.125
10	Staph. 503	0.062	2	0.125	0.125	0.125
	Kl.aerog. 1082E	0.5	1	0.5	0.5	0.5
	Citrob. 82 Cull. 1		2	0.5	0.5	0.25

15 Example 2

Action of the combination of (1) and (2) towards clinical isolates resistant to the cephalosporin component.

Table 2

		<u>MIC in mg/l</u>				
		(1)	(2)	(1) : (2)		
	<u>Pathogen</u>	alone	alone	1:1	1:2	1:3
25	Staph. 789	4	64	4	4	8
	Staph. 22130	2	32	4	4	4
	Strept. D 756	8	64	4	4	4
	Strept. D Eder	8	64	4	4	4
	Strept.faecium D	8	64	8	16	8
30	Citrob. 2901	8	64	4	4	4
	Ent. cl. M 423	4	64	2	2	4
	Ent. cl. M. 447	16	64	16	8	8
	Ent. cl. P99	2	64	2	2	2

Example 3

Action of the combination of (1) and (2) on anaerobic pathogens

5

Table 3

	Pathogen	MIC in mg/l				
		(1) alone	(2) alone	(1) : (2)		
10				1:1	1:2	1:3
	B.fragilis 312	0.125	128	0.125	0.25	0.25
	B.fragilis 960	0.125	16	0.125	0.125	0.125
	B.fragilis 17390	0.25	8	0.25	0.5	0.25
	B.fragilis 18125	0.25	2	0.25	0.25	0.25
15	B.ovatus 103	0.125	64	0.125	0.125	0.125
	B.vulgatus 1446	0.125	64	0.125	0.125	0.125
	B.thetaiotaomicron 123	0.125	64	0.125	0.125	0.125
	Sph. varius 5262	0.25	64	0.5	1	1
20	Cl. tetani 19406	0.25	8	0.5	0.5	0.5

Example 4

The combination of the potassium salt of the penem compound 5R,6S-3-(2-carbamoyloxy-ethylthio)-6-(1R-hydroxy-ethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-carboxylic acid (3) with compound (2) was tested on 3 strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

Table 4

FIC values of a combination of the	
<u>penem (3) with the cephalosporin (2)</u>	
Strain	
5 E. coli 2136E	0.5
E. coli 2137E	0.75*
E. coli 2138E	0.5
Citrobacter freundii 8090	0.281

- 10 * The FIC value of 0.75 indicates a hyperadditive action.

Example 5

- 15 The combination of the potassium salt of the penem compound 5R,6S-6-(1R-hydroxyethyl)-3-(4-formamidophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (4) with compound (2) was tested on 3 strains of E. coli and one strain of Citrobacter freundii. The
- 20 "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values
- 25 of 1 show an additive interaction.

Table 5

FIC values of a combination of the	
<u>penem (4) with the cephalosporin (2)</u>	
Strain	
30 E. coli 2136E	0.5
E. coli 2137E	0.375
E. coli 2138E	0.5
Citrobacter freundii 8090	0.091

35

Example 6

The combination of the sodium salt of the penem compound 5R,6S-3-(3-carbamoylphenyl)-6-(1R-hydroxyethyl)-7-oxo-4-

thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (5) with compound (2) was tested on 3 strains of *E. coli* and one strain of *Citrobacter freundii*. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

Table 6

FIC values of a combination of the	
<u>Strain</u> <u>penem (5) with the cephalosporin (2)</u>	
15 <i>E. coli</i> 2136E	0.375
<i>E. coli</i> 2137E	0.5
<i>E. coli</i> 2138E	0.375
<i>Citrobacter freundii</i> 8090	0.125

20 Example 7

The activity of cephalosporins, such as are indicated above as an example, towards Gram-positive pathogens such as staphylococci and towards Gram-negative anaerobic pathogens is in most cases lower than that towards Gram-negative aerobic pathogenic organisms (see also Seibert et al., Infection, Volume 11 (1983) 5, 275-279).

30 By contrast, penems have as a rule a higher antibacterial activity towards Gram-positive cocci and anaerobics than towards Gram-negative pathogens (see also Bauernfeind, J. Antimicrob. Chemother 15, 111, 1985).

35 Taking a combination of one part of a penem and three parts of a cephalosporin as an example, Table 7 shows a superiority of the antibacterial activity of the combination as compared with the individual components. The combination product evens out the weakness in the antibacterial spectrum of the two products and thus has a

broader antibacterial spectrum which makes it particularly suitable for a therapy of bacterial infections without preceding isolation of the causative organism.

5

Table 7

	Strain	HRE 664 (1)	<u>MIC in mg/l</u>	
			Cefotaxim (2)	(1) : (2) 1:3
10	Strept. D 756	8	64	4
	Strept. D Eder	8	64	4
	Strept. D 21777	8	64	4
	Strept. D 26777	8	64	4
	Citrob. 2901	8	64	4
15	Citrob. 82 Cull.	1	2	0.25
	Ent. cl. M 447	16	64	8
	Ent. cl. 2240 Cull.	2	0.062	0.015
	E. coli 2139E	1	0.031	0.015
	Kl. pneu. 1976E	1	0.062	0.031
20	B. vulgatus 1446	0.125	64	0.125
	B. distasonis 1366	0.25	0.125	0.125

Example 8

- 25 The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(4-carbamoyl-phenoxy)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (1) with cefotaxim was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC
- 30 index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

to 199200000

Strain	FIC index
E. coli 2136E	0.312
E. coli 2137E	0.312
E. coli 2138E	0.249
5 Citrobacter freundii 8090	0.094

Example 9

10 The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(4-methyl-sulfinylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (6) with cefotaxim (2) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was deter-

15 mined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

Strain	FIC index
20 E. coli 2136E	0.379
E. coli 2137E	0.5
E. coli 2138E	0.282
Citrobacter freundii 8090	0.5

25

Example 10

30 The combination of sodium 5R,6S-3-(4-methylsulfinylphenoxy)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (7) with cefotaxim (2) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

35

	Strain	FIC index
	E. coli 2136E	0.379
	E. coli 2137E	0.320
	E. coli 2138E	0.374
5	Citrobacter freundii 8090	0.047

Example 11

The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(3-sulfamoyl-propylthio)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (8) with cefotaxim (2) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

20

	Strain	FIC index
	E. coli 2136E	0.379
	E. coli 2137E	0.379
	E. coli 2138E	0.379
25	Citrobacter freundii 8090	0.312

Example 12

The combination of potassium 5R,6S-6-(1R-hydroxyethyl)-3-(3-methylsulfinylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (9) with cefotaxim (2) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

35

	Strain	FIC index
	E. coli 2136E	0.383
	E. coli 2137E	0.383
	E. coli 2138E	0.185
5	Citrobacter freundii 8090	0.0935

Example 13

10 The combination of sodium 5R,6S-3-(4-cyanophenoxy)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (10) with cefotaxim (2) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by 15 the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

	Strain	FIC index
20	E. coli 2136E	0.5
	E. coli 2137E	0.25
	E. coli 2138E	0.25
	Citrobacter freundii 8090	0.75

25

Example 14

30 The combination of the sodium salt of 5R,6S-6-(1R-hydroxyethyl)-3-(4-carbamoyl-phenoxy)-7-oxo-4-thia-1-azobicyclo[3.2.0]hept-2-ene-carboxylic acid (1) with cefodizim (11) was tested on three strains of E. coli. and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. Accord- 35 ing to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

	Strain	FIC index
	<i>E. coli</i> 2136E	0.49
	<i>E. coli</i> 2137E	0.5
	<i>E. coli</i> 2138E	0.37
5	<i>Citrobacter freundii</i>	0.186

Example 15

10 The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(4-methyl-sulfinylphenyl)-7-oxo-4-thia-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate (6) with cefodizim (11) was tested on three strains of *E. coli* and one strain of *Citrobacter freundii*. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

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	Strain	FIC index
	<i>E. coli</i> 2136E	0.155
	<i>E. coli</i> 2137E	0.498
	<i>E. coli</i> 2138E	0.374
25	<i>Citrobacter freundii</i> 8090	0.375

Example 16

30 The combination of sodium 5R,6S-3-(4-methylsulfinylphenoxy)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate (7) with cefodizim (11) was tested on three strains of *E. coli* and one strain of *Citrobacter freundii*. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

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	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.5
	E. coli 2138E	0.249
5	Citrobacter freundii 8090	0.140

Example 17

10 The combination of potassium 5R,6S-6-(1R-hydroxyethyl)-
3-(3-methylsulfinylphenyl)-7-oxo-4-thia-1-azabicyclo-
[3.2.0]hept-2-ene-2-carboxylate (9) with cefodizim (11)
was tested on three strains of E. coli and one strain of
Citrobacter freundii. The "fractional inhibitory con-
centration" (FIC index) as a measure of the synergistic
15 activity was determined by the method of Berenbaum, J.
Infect. Dis. 137 (1978), 122-136. According to this
publication, FIC values of ≤ 0.5 are characteristic of
a synergistic activity, and FIC values of 1 show an
additive interaction.

20

	Strain	FIC index
	E. coli 2136E	0.125
	E. coli 2137E	0.187
	E. coli 2138E	0.375
25	Citrobacter freundii 8090	0.093

Example 18

30 The combination of sodium 5R,6S-3-(4-cyanophenoxy)-6-(1R-
hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-
ene-2-carboxylate (10) with cefodizim (11) was tested on
three strains of E. coli and one strain of Citrobacter
freundii. The "fractional inhibitory concentration"
(FIC index) as a measure of the synergistic activity was
35 determined by the method of Berenbaum, J. Infect. Dis.
137 (1978), 122-136. According to this publication, FIC
values of ≤ 0.5 are characteristic of a synergistic activ-
ity, and FIC values of 1 show an additive interaction.

	Strain	FIC index
	<i>E. coli</i> 2136E	0.75
	<i>E. coli</i> 2137E	0.373
	<i>E. coli</i> 2138E	0.498
5	<i>Citrobacter freundii</i> 8090	0.062

Example 19

The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(3-sulfamoyl-propylthio)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (8) with cefodizim (11) was tested on three strains of *E. coli* and one strain of *Citrobacter freundii*. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

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	Strain	FIC index
	<i>E. coli</i> 2136E	0.498
	<i>E. coli</i> 2137E	0.498
	<i>E. coli</i> 2138E	0.624
25	<i>Citrobacter freundii</i> 8090	0.281

Example 20

The combination of sodium 5R,6S-3-(3-carbamoylphenyl)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (5) with cefodizim (11) was tested on three strains of *E. coli* and one strain of *Citrobacter freundii*. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

	Strain	FIC index
	<i>E. coli</i> 2136E	0.75
	<i>E. coli</i> 2137E	0.496
	<i>E. coli</i> 2138E	1
5	<i>Citrobacter freundii</i> 8090	0.187

Example 21

10 The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(2-carbamoyl-oxyethylthio)-7-oxo-4-thia-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate (3) with cefodizim (11) was tested on three strains of *E. coli* and one strain of *Citrobacter freundii*. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

20

	Strain	FIC index
	<i>E. coli</i> 2136E	0.498
	<i>E. coli</i> 2137E	0.498
	<i>E. coli</i> 2138E	0.5
25	<i>Citrobacter freundii</i> 8090	0.249

Example 22

30 The combination of potassium 5R,6S-6-(1R-hydroxyethyl)-3-(4-formamidophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (4) with cefodizim (11) was tested on three strains of *E. coli* and one strain of *Citrobacter freundii*. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

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	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.75
	E. coli 2138E	0.5
5	Citrobacter freundii 8090	0.125

Example 23

10 The combination of the sodium salt of 5R,6S-6-(1R-hydroxy-ethyl)-3-(4-carbamoyl-phenoxy)-7-oxo-4-thia-1-azabicyclo-
[3.2.0]hept-2-ene-2-carboxylic acid (1) with cefpirome
(12) was tested on three strains of E. coli. and one strain of
Citrobacter freundii. The "fractional inhibitory concentration" (FIC index)
as a measure of the synergistic activity was determined by the
15 method of Berenbaum, J. Infect. Dis. 137 (1978), 122-
136. According to this publication, FIC values of ≤ 0.5
are characteristic of a synergistic activity, and FIC
values of 1 show an additive interaction.

20	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.66
	E. coli 2138E	0.315
	Citrobacter freundii	0.5

25

Example 24

30 The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(4-methylsulfinylphenyl)-7-oxo-4-thia-1-azabicyclo-
[3.2.0]hept-2-ene-2-carboxylate (6) with cefpirome (12)
was tested on three strains of E. coli and one strain of
Citrobacter freundii. The "fractional inhibitory con-
centration" (FIC index) as a measure of the synergistic
activity was determined by the method of Berenbaum, J.
35 Infect. Dis. 137 (1978), 122-136. According to this
publication, FIC values of ≤ 0.5 are characteristic of
a synergistic activity, and FIC values of 1 show an
additive interaction.

Strain	FIC index
E. coli 2136E	0.374
E. coli 2137E	0.249
E. coli 2138E	0.187
5 Citrobacter freundii 8090	0.126

Example 25

The combination of sodium 5R,6S-3-(4-methylsulfinylphen-
 10 oxy)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-
 hept-2-ene-2-carboxylate (7) with cefpirome (12) was
 tested on three strains of E. coli and one strain of
 Citrobacter freundii. The "fractional inhibitory con-
 centration" (FIC index) as a measure of the synergistic
 15 activity was determined by the method of Berenbaum, J.
 Infect. Dis. 137 (1978), 122-136. According to this
 publication, FIC values of ≤ 0.5 are characteristic of
 a synergistic activity, and FIC values of 1 show an
 additive interaction.

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Strain	FIC index
E. coli 2136E	0.629
E. coli 2137E	0.5
E. coli 2138E	0.5
25 Citrobacter freundii 8090	0.126

Example 26

The combination of potassium 5R,6S-6-(1R-hydroxyethyl)-
 30 3-(3-methylsulfinylphenyl)-7-oxo-4-thia-1-azabicyclo-
 [3.2.0]hept-2-ene-2-carboxylate (9) with cefpirome (12)
 was tested on three strains of E. coli and one strain of
 Citrobacter freundii. The "fractional inhibitory con-
 35 centration" (FIC index) as a measure of the synergistic
 activity was determined by the method of Berenbaum, J.
 Infect. Dis. 137 (1978), 122-136. According to this
 publication, FIC values of ≤ 0.5 are characteristic of
 a synergistic activity, and FIC values of 1 show an
 additive interaction.

	Strain	FIC index
	E. coli 2136E	0.125
	E. coli 2137E	0.5
	E. coli 2138E	0.186
5	Citrobacter freundii 8090	0.258

Example 27

10 The combination of sodium 5R,6S-3-(4-cyanophenoxy)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (10) with cefpirome (12) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined
15 by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

20	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.5
	E. coli 2138E	0.5
	Citrobacter freundii 8090	0.062

25

Example 28

30 The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(3-sulfamoyl-propylthio)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (8) with cefpirome (12) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J.
35 Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

	Strain	FIC index
	E. coli 2136E	0.75
	E. coli 2137E	0.62
	E. coli 2138E	0.5
5	Citrobacter freundii 8090	0.5

Example 29

10 The combination of sodium 5R,6S-3-(3-carbamoyl-phenyl)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (5) with cefpirome(12) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was
15 determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

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	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.75
	E. coli 2138E	0.372
25	Citrobacter freundii 8090	0.390

Example 30

30 The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(2-carbamoyloxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (3) with cefpirome(12) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was
35 determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

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	Strain	FIC index
	E. coli 2136E	0.366
	E. coli 2137E	0.496
	E. coli 2138E	0.372
5	Citrobacter freundii 8090	0.366

Example 31

10 The combination of potassium 5R,6S-6-(1R-hydroxyethyl)-
3-(4-formamidophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-
hept-2-ene-2-carboxylate (4) with cefpirome (12) was tested
on three strains of E. coli and one strain of Citrobacter
freundii. The "fractional inhibitory concentration"
15 (FIC index) as a measure of the synergistic activity was
determined by the method of Berenbaum, J. Infect. Dis.
137 (1978), 122-136. According to this publication, FIC
values of ≤ 0.5 are characteristic of a synergistic acti-
vity, and FIC values of 1 show an additive interaction.

20	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.5
	E. coli 2138E	0.312
	Citrobacter freundii 8090	0.125

25

Example 32

30 The combination of the sodium salt of 5R,6S-6-(1R-hy-
droxyethyl)-3-(4-carbamoyl-phenoxy)-7-oxo-4-thia-1-aza-
bicyclo[3.2.0]hept-2-ene-2-carboxylic acid (1) with cef-
triaxon (13) was tested on three strains of E. coli. and one
strain of Citrobacter freundii. The "fractional inhibitory concentration"
(FIC index) as a measure of the synergistic activity was determined
by the method of Berenbaum, J. Infect. Dis. 137 (1978),
35 122-136. According to this publication, FIC values of
 ≤ 0.5 are characteristic of a synergistic activity, and
FIC values of 1 show an additive interaction.

	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.379
	E. coli 2138E	0.75
5	Citrobacter freundii 8090	0.075

Example 33

10 The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(4-methylsulfinylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (6) with ceftriaxon (13) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

20

	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.498
	E. coli 2138E	0.374
25	Citrobacter freundii 8090	0.187

Example 34

30 The combination of sodium 5R,6S-3-(4-methylsulfinylphenoxy)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (7) with ceftriaxon (13) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

35

	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.5
	E. coli 2138E	0.75
5	Citrobacter freundii 8090	0.091

Example 35

The combination of potassium 5R,6S-6-(1R-hydroxyethyl)-
 10 3-(3-methylsulfinylphenyl)-7-oxo-4-thia-1-azabicyclo-
 [3.2.0]hept-2-ene-2-carboxylate (9) with ceftriaxon (13)
 was tested on three strains of E. coli and one strain of
 Citrobacter freundii. The "fractional inhibitory con-
 centration" (FIC index) as a measure of the synergistic
 15 activity was determined by the method of Berenbaum, J.
 Infect. Dis. 137 (1978), 122-136. According to this
 publication, FIC values of ≤ 0.5 are characteristic of
 a synergistic activity, and FIC values of 1 show an
 additive interaction.

20

	Strain	FIC index
	E. coli 2136E	0.125
	E. coli 2137E	0.75
	E. coli 2138E	0.077
25	Citrobacter freundii 8090	0.034

Example 36

The combination of sodium 5R,6S-3-(4-cyanophenoxy)-6-(1R-
 30 hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-
 ene-2-carboxylate (10) with ceftriaxon (13) was tested on
 three strains of E. coli and one strain of Citrobacter
 freundii. The "fractional inhibitory concentration"
 (FIC index) as a measure of the synergistic activity was
 35 determined by the method of Berenbaum, J. Infect. Dis.
 137 (1978), 122-136. According to this publication, FIC
 values of ≤ 0.5 are characteristic of a synergistic activ-
 ity, and FIC values of 1 show an additive interaction.

	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.5
	E. coli 2138E	0.5
5	Citrobacter freundii 8090	0.182

Example 37

10 The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(3-sulfamoyl-propylthio)-7-oxo-4-thia-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate (8) with ceftriaxon (13) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

20

	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.5
	E. coli 2138E	0.5
25	Citrobacter freundii 8090	0.186

Example 38

30 The combination of sodium 5R,6S-3-(3-carbamoyl-phenyl)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (5) with ceftriaxon (13) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

35

	Strain	FIC index
	E. coli 2136E	0.318
	E. coli 2137E	0.31
	E. coli 2138E	0.75
5	Citrobacter freundii 8090	0.06

Example 39

10 The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(2-carbamoyloxyethylthio)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (3) with ceftriaxon (13) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

20

	Strain	FIC index
	E. coli 2136E	0.75
	E. coli 2137E	0.75
	E. coli 2138E	0.629
25	Citrobacter freundii	0.0625

Example 40

30 The combination of potassium 5R,6S-6-(1R-hydroxyethyl)-3-(4-formamidophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (4) with ceftriaxon (13) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

35

	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.125
	E. coli 2138E	0.5
5	Citrobacter freundii 8090	0.372

Example 41

10 The combination of the sodium salt of 5R,6S-6-(1R-hydroxyethyl)-3-(4-carbamoyl-phenoxy)-7-oxo-4-thia-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic acid (1) with cefotiam (14) was tested on three strains of E. coli. and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of
15 Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

20	Strain	FIC index
	E. coli 2136E	0.49
	E. coli 2137E	0.5
	E. coli 2138E	0.372
	Citrobacter freundii	0.077

25

Example 42

The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(4-methylsulfinylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-
30 hept-2-ene-2-carboxylate (6) with cefotiam (14) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis.
35 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

	Strain	FIC index
	E. coli 2136E	0.312
	E. coli 2137E	0.375
	E. coli 2138E	0.374
5	Citrobacter freundii 8090	0.312

Example 43

10 The combination of sodium 5R,6S-3-(4-methylsulfinylphen-
oxy)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo-
[3.2.0]hept-2-ene-2-carboxylate (7) with cefotiam (14)
was tested on three strains of E. coli and one strain of
Citrobacter freundii. The "fractional inhibitory con-
centration" (FIC index) as a measure of the synergistic
15 activity was determined by the method of Berenbaum, J.
Infect. Dis. 137 (1978), 122-136. According to this
publication, FIC values of ≤ 0.5 are characteristic of
a synergistic activity, and FIC values of 1 show an
additive interaction.

20

	Strain	FIC index
	E. coli 2136E	0.498
	E. coli 2137E	0.5
	E. coli 2138E	0.374
25	Citrobacter freundii 8090	0.077

Example 44

30 The combination of potassium 5R,6S-6-(1R-hydroxyethyl)-3-
(3-methylsulfinylphenyl)-7-oxo-4-thia-1-azabicyclo-
[3.2.0]hept-2-ene-2-carboxylate (9) with cefotiam (14)
was tested on three strains of E. coli and one strain of
Citrobacter freundii. The "fractional inhibitory con-
centration" (FIC index) as a measure of the synergistic
35 activity was determined by the method of Berenbaum, J.
Infect. Dis. 137 (1978), 122-136. According to this
publication, FIC values of ≤ 0.5 are characteristic of
a synergistic activity, and FIC values of 1 show an
additive interaction.

	Strain	FIC index
	E. coli 2136E	0.75
	E. coli 2137E	0.75
	E. coli 2138E	0.5
5	Citrobacter freundii 8090	0.125

Example 45

10 The combination of sodium 5R,6S-3-(4-cyanophenoxy)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (10) with cefotiam (14) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined
15 by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

20	Strain	FIC index
	E. coli 2136E	1
	E. coli 2137E	0.375
	E. coli 2138E	0.375
	Citrobacter freundii 8090	0.186

25

Example 46

30 The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(3-sulfamoylpropylthio)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (8) with cefotiam (14) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis.
35 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

	Strain	FIC index
	E. coli 2136E	0.63
	E. coli 2137E	0.75
	E. coli 2138E	0.5
5	Citrobacter freundii 8090	0.265

Example 47

10 The combination of sodium 5R,6S-3-(3-carbamoyl-phenyl)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (5) with cefotiam (14) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was
 15 determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

20	Strain	FIC index
	E. coli 2136E	0.75
	E. coli 2137E	0.5
	E. coli 2138E	0.5
	Citrobacter freundii 8090	0.186

25

Example 48

30 The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(2-carbamoyloxyethylthio)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (3) with cefotiam (14) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was
 35 determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.498
	E. coli 2138E	0.498
5	Citrobacter freundii 8090	0.124

Example 49

10 The combination of potassium 5R,6S-6-(1R-hydroxyethyl)-3-(4-formamidophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (4) with cefotiam (14) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was
15 determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

20	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.5
	E. coli 2138E	0.624
	Citrobacter freundii 8090	0.156

25

Example 50

30 The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(4-carbamoyl-phenoxy)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (1) with cefoperazon (15) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J.
35 Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.5
	E. coli 2138E	0.278
5	Citrobacter freundii 8090	0.09

Example 51

10 The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(4-methylsulfinylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (6) with cefoperazon (15) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

20

	Strain	FIC index
	E. coli 2136E	0.25
	E. coli 2137E	0.75
	E. coli 2138E	0.498
25	Citrobacter freundii 8090	0.056

Example 52

30 The combination of sodium 5R,6S-3-(4-methylsulfinylphenoxy)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (7) with cefoperazon (15) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

35

	Strain	FIC index
	E. coli 2136E	0.75
	E. coli 2137E	0.75
	E. coli 2138E	0.374
5	Citrobacter freundii 8090	0.077

Example 53

10 The combination of potassium 5R,6S-6-(1R-hydroxyethyl)-3-(3-methylsulfinylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (9) with cefoperazon (15) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

20

	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.5
	E. coli 2138E	0.75
25	Citrobacter freundii 8090	0.312

Example 54

30 The combination of sodium 5R,6S-3-(4-cyanophenoxy)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (10) with cefoperazon (15) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.25
	E. coli 2138E	0.28
5	Citrobacter freundii 8090	0.091

Example 55

10 The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(3-sulfamoyl-propylthio)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (8) with cefoperazon (15) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

20

	Strain	FIC index
	E. coli 2136E	0.75
	E. coli 2137E	0.75
	E. coli 2138E	0.373
25	Citrobacter freundii 8090	0.281

Example 56

30 The combination of sodium 5R,6S-3-(3-carbamoylphenyl)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (5) with cefoperazon (15) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

35

	Strain	FIC index
	E. coli 2136E	0.31
	E. coli 2137E	0.374
	E. coli 2138E	0.308
5	Citrobacter freundii 8090	0.124

Example 57

10 The combination of sodium 5R,6S-6-(1R-hydroxyethyl)-3-(2-carbamoyloyxethylthio)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (3) with cefoperazon (15) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

20

	Strain	FIC index
	E. coli 2136E	0.563
	E. coli 2137E	1.
	E. coli 2138E	0.5
25	Citrobacter freundii 8090	0.366

Example 58

30 The combination of potassium 5R,6S-6-(1R-hydroxyethyl)-3-(4-formamidophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (4) with cefoperazon (15) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

35

	Strain	FIC index
	E. coli 2136E	0.75
	E. coli 2137E	0.75
	E. coli 2138E	0.372
5	Citrobacter freundii 8090	0.248

Example 59

10 The combination of sodium 5R,6S-3-(4-formamido-phenoxy)-
6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-
2-ene-2-carboxylate (16) with cefotaxim (2) was tested
on three strains of E. coli and one strain of Citrobacter
freundii. The "fractional inhibitory concentration"
15 (FIC index) as a measure of the synergistic activity was
determined by the method of Berenbaum, J. Infect. Dis.
137 (1978), 122-136. According to this publication, FIC
values of ≤ 0.5 are characteristic of a synergistic acti-
vity, and FIC values of 1 show an additive interaction.

20	Strain	FIC index
	E. coli 2136E	0.383
	E. coli 2137E	0.5
	E. coli 2138E	0.374
	Citrobacter freundii 8090	0.122

25

Example 60

30 The combination of sodium 5R,6S-3-(4-formamido-phenoxy)-
6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-
2-ene-2-carboxylate (16) with cefodizim (11) was tested
on three strains of E. coli and one strain of Citrobacter
freundii. The "fractional inhibitory concentration"
(FIC index) as a measure of the synergistic activity was
determined by the method of Berenbaum, J. Infect. Dis.
35 137 (1978), 122-136. According to this publication, FIC
values of ≤ 0.5 are characteristic of a synergistic acti-
vity, and FIC values of 1 show an additive interaction.

	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.5
	E. coli 2138E	0.125
5	Citrobacter freundii 8090	0.047

Example 61

10 The combination of sodium 5R,6S-3-(4-formamido-phenoxy)-
6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-
2-ene-2-carboxylate (16) with cefpirome (12) was tested
on three strains of E. coli and one strain of Citrobacter
freundii. The "fractional inhibitory concentration"
15 (FIC index) as a measure of the synergistic activity was
determined by the method of Berenbaum, J. Infect. Dis.
137 (1978), 122-136. According to this publication, FIC
values of ≤ 0.5 are characteristic of a synergistic acti-
vity, and FIC values of 1 show an additive interaction.

	Strain	FIC index
20	E. coli 2136E	0.5
	E. coli 2137E	0.5
	E. coli 2138E	0.5
	Citrobacter freundii 8090	0.273

25

Example 62

30 The combination of sodium 5R,6S-3-(4-formamido-phenoxy)-
6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-
2-ene-2-carboxylate (16) with ceftriaxon (13) was tested
on three strains of E. coli and one strain of Citrobacter
freundii. The "fractional inhibitory concentration"
(FIC index) as a measure of the synergistic activity was
determined by the method of Berenbaum, J. Infect. Dis.
35 137 (1978), 122-136. According to this publication, FIC
values of ≤ 0.5 are characteristic of a synergistic acti-
vity, and FIC values of 1 show an additive interaction.

	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.5
	E. coli 2138E	0.36
5	Citrobacter freundii 8090	0.122

Example 63

10 The combination of sodium 5R,6S-3-(4-formamido-phenoxy)-
6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-
2-ene-2-carboxylate (16) with cefotiam (14) was tested on
three strains of E. coli and one strain of Citrobacter
freundii. The "fractional inhibitory concentration"
15 (FIC index) as a measure of the synergistic activity was
determined by the method of Berenbaum, J. Infect. Dis.
137 (1978), 122-136. According to this publication, FIC
values of ≤ 0.5 are characteristic of a synergistic acti-
vity, and FIC values of 1 show an additive interaction.

20	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.374
	E. coli 2138E	0.374
	Citrobacter freundii 8090	0.257

25

Example 64

30 The combination of sodium 5R,6S-4-(4-formamido-phenoxy)-
6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-
2-ene-2-carboxylate (16) with cefoperazon (15) was tested
on three strains of E. coli and one strain of Citrobacter
freundii. The "fractional inhibitory concentration"
(FIC index) as a measure of the synergistic activity was
35 determined by the method of Berenbaum, J. Infect. Dis.
137, (1978), 122-136. According to this publication, FIC
values of ≤ 0.5 are characteristic of a synergistic acti-
vity, and FIC values of 1 show an additive interaction.

	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.75
	E. coli 2138E	0.5
5	Citrobacter freundii 8090	0.093

Example 65

10 The combination of sodium 5R,6S-3-(carbamoyloxymethyl)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (17) with cefotaxim (2) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was
15 determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

20	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.37
	E. coli 2138E	0.5
	Citrobacter freundii 8090	0.122

25

Example 66

30 The combination of sodium 5R,6S-3-(carbamoyloxymethyl)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (17) with cefodizim (11) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was
35 determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

	Strain	FIC index
	E. coli 2136E	0.5
	E. coli 2137E	0.5
	E. coli 2138E	0.75
5	Citrobacter freundii 8090	0.125

Example 67

The combination of sodium 5R,6S-3-(carbamoyloxymethyl)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (17) with cefpirome (12) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

	Strain	FIC index
	E. coli 2136E	0.37
	E. coli 2137E	0.5
	E. coli 2138E	0.5
	Citrobacter freundii 8090	0.062

25

Example 68

The combination of sodium 5R,6S-3-(carbamoyloxymethyl)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (17) with ceftriaxon (13) was tested on three strains of E. coli and one strain of Citrobacter freundii. The "fractional inhibitory concentration" (FIC index) as a measure of the synergistic activity was determined by the method of Berenbaum, J. Infect. Dis. 137 (1978), 122-136. According to this publication, FIC values of ≤ 0.5 are characteristic of a synergistic activity, and FIC values of 1 show an additive interaction.

Strain	FIC index
E. coli 2136E	0.375
E. coli 2137E	0.125
E. coli 2138E	0.5
5 Citrobacter freundii 8090	0.093

Example 69

Preparation of a parenteral formulation

10

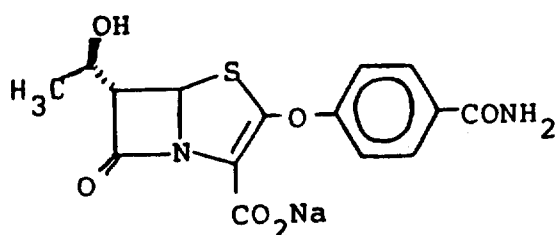
1.5 g of cefotaxim (2) and 0.5 g of HRE 664 (1) are dissolved in 10 ml of water ad injec. and then administered.

15

Depending on the solubility properties, similar quantity ratios are also applicable to the other illustrative examples described above.

Compounds of the illustrative examples

20



Compound number

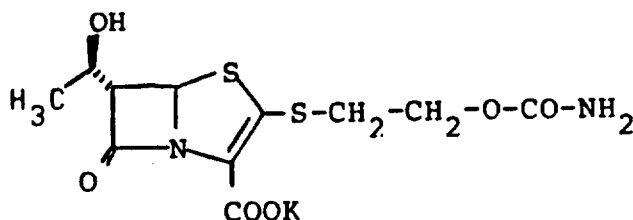
(1)

HRE 664

25

5R,6S-6-((1R)-Hydroxyethyl)-3-(4-carbamoyl-phenoxy)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (sodium salt)

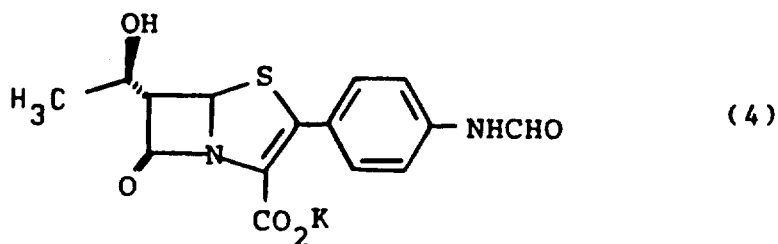
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(3)

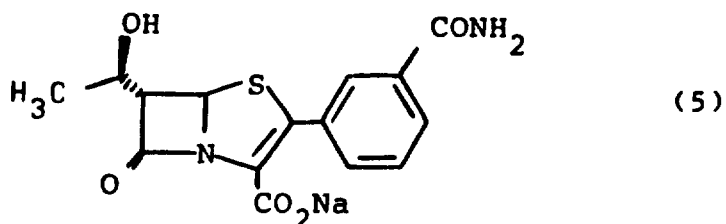
35

5R,6S-3-(2-Carbamoyloxyethylthio)-6-((1R)-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (potassium salt)



5R,6S-6-(1R-Hydroxyethyl)-3-(4-formamidophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (potassium salt)

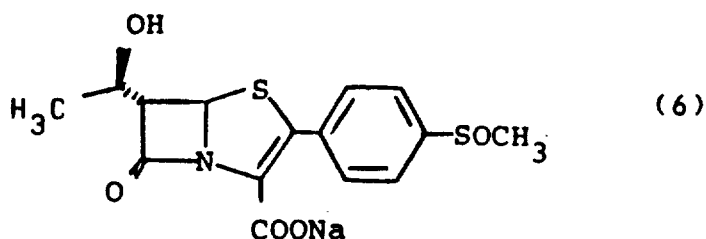
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15

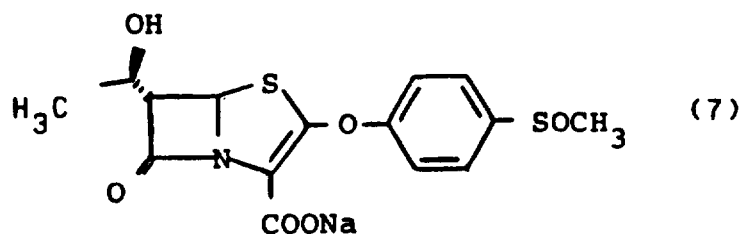
5R,6S-3-(3-Carbamoyl-phenyl)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (sodium salt)

20

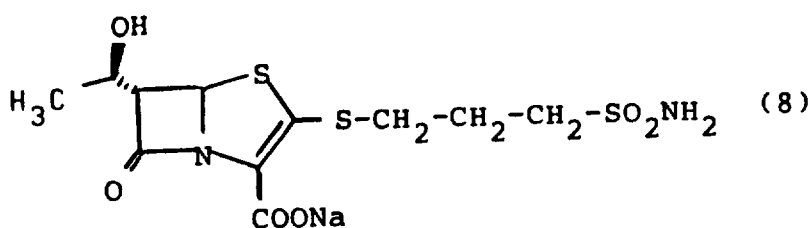


25 5R,6S-6-(1R-Hydroxyethyl)-3-(4-methylsulfinyl-phenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (sodium salt)

30

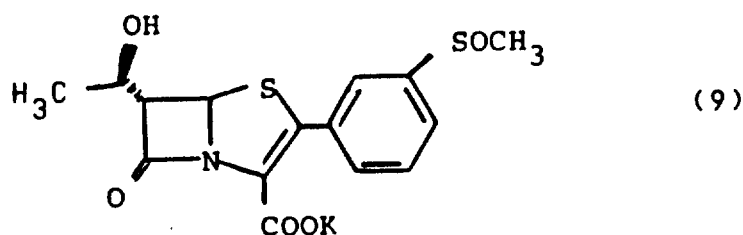


35 5R,6S-3-(4-Methylsulfinyl-phenoxy)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (sodium salt)



5R,6S-6-(1R-Hydroxyethyl)-3-(3-sulfamoyl-propylthio)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (sodium salt)

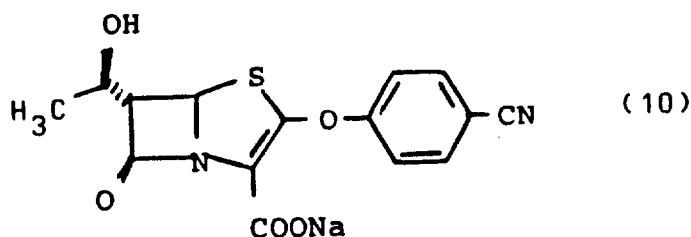
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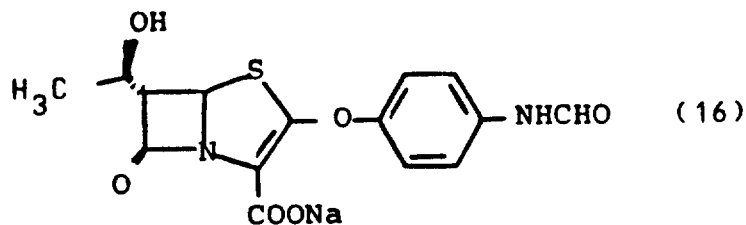
5R,6S-6-(1R-Hydroxyethyl)-3-(3-methylsulfinyl-phenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (potassium salt)

20



25 5R,6S-3-(4-Cyanophenoxy)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (sodium salt)

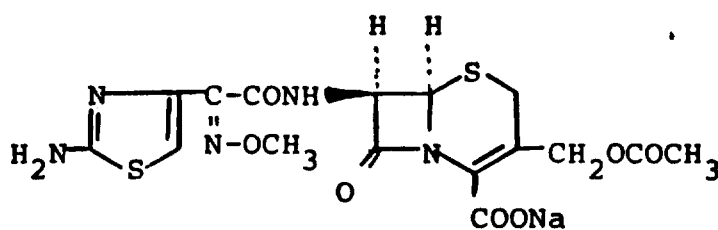
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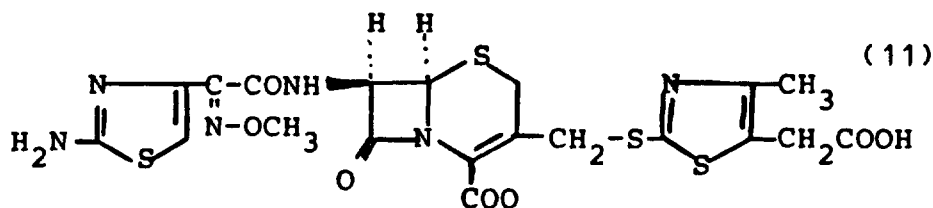
5R,6S-3-(4-Formamido-phenoxy)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (sodium salt)

35

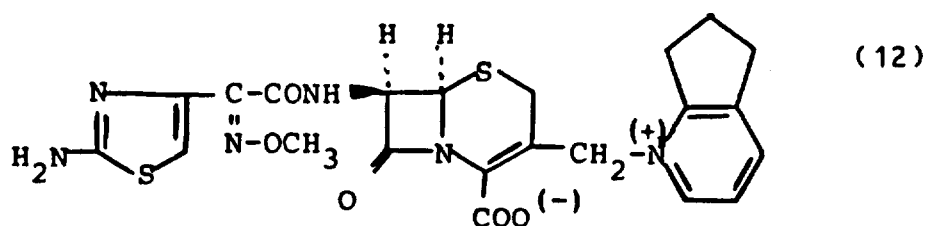
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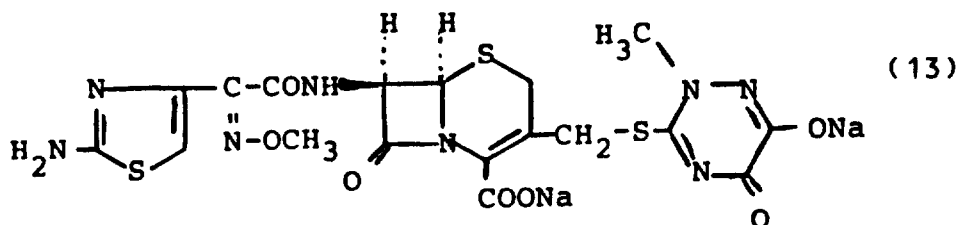
Cefotaxim (sodium salt)



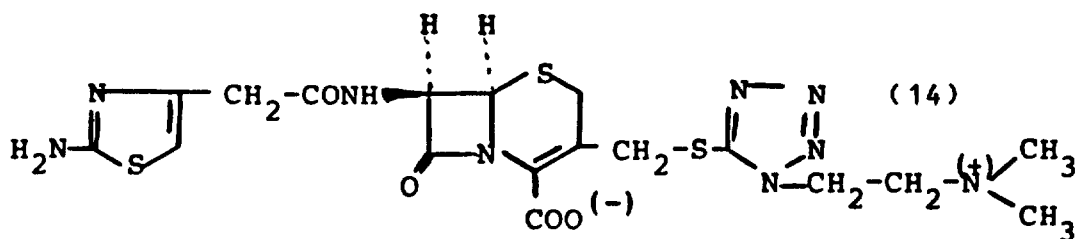
Cefodizim (sodium salt)



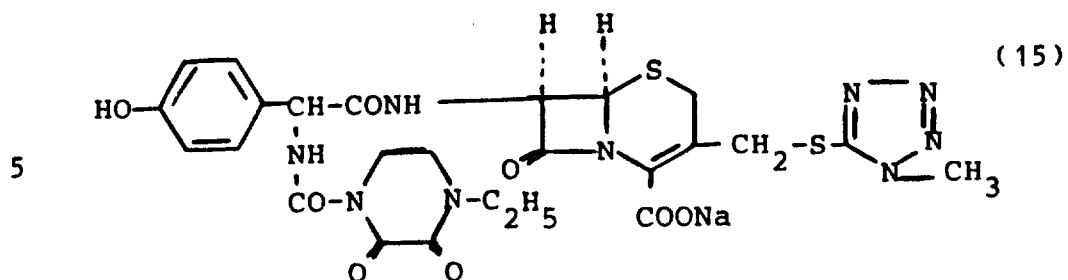
Cefpirom



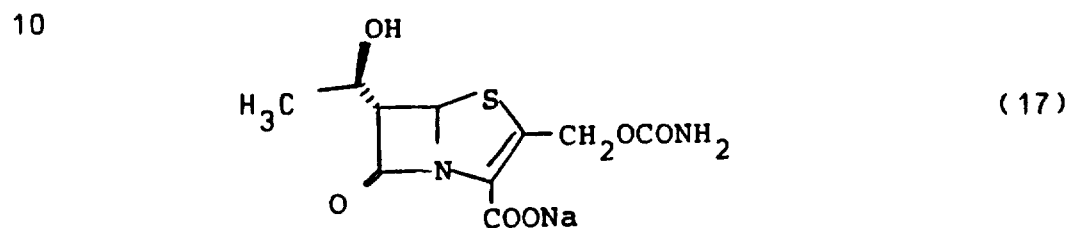
Ceftriaxon (disodium salt)



Cefotiam



Cefoperazon (sodium salt)



15

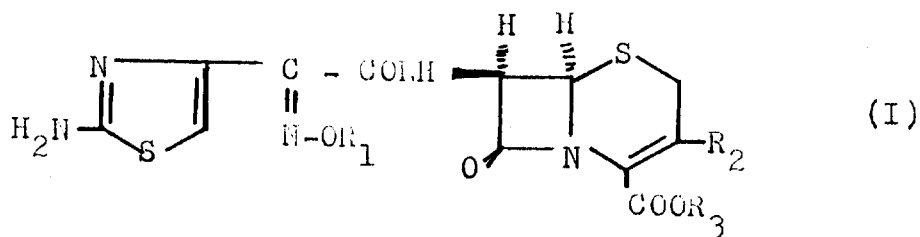
5R,6S-3-((Carbamoyloxymethyl)-6-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (sodium salt)

PATENT CLAIMS:

1. An improved pharmaceutical formulation having a synergistic antibacterial activity, comprising

a) a cephalosporin derivative of the formula

I



in which

R_1 denotes

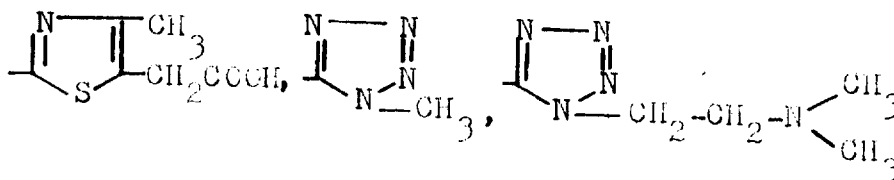
C_1-C_4 -alkyl and the

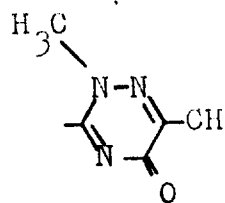
$=N-OR_1$ group is in the syn position,

R_2 has the meaning of acetoxyethyl,

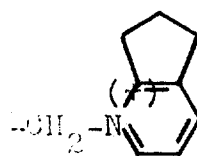
$-CH_2S-X$,

with $X =$



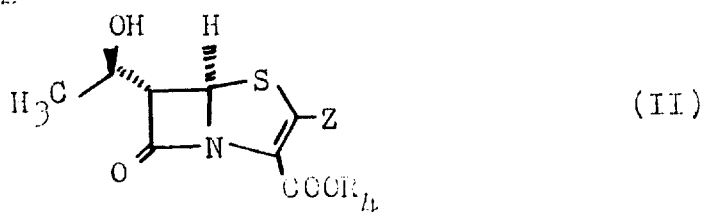


or of

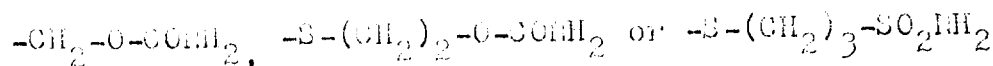
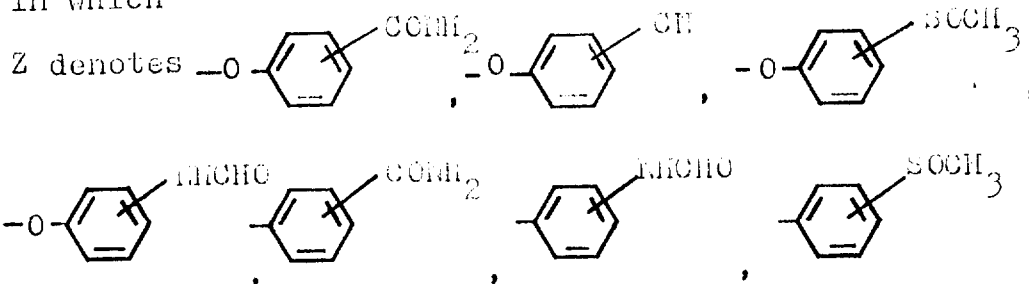


and

R_3 is hydrogen, a physiologically acceptable cation, a physiologically acceptable ester radical or - if the structure $-CH_2-\overset{(+)}{N}$ appears in R_2- represents a negative charge, and



in which



and

R_4 is hydrogen, a physiologically acceptable cation or a physiologically acceptable ester radical.

in a ratio between 1:9 and 9:1.

2. A formulation as claimed in claim 1, wherein the cephalosporin derivative is an 1-acetyl-phenylglycinecephalosporin.

3. A formulation as claimed in claim 1, wherein

$-CH_2-$ takes the place of $-C(=CH-CH_1)$ in formula (1).

- [54] Title: PHARMACEUTICAL FORMULATION FOR THE TREATMENT OF BACTERIAL INFECTIONS
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- [73] Assignee (s): HOECHST AKTIENGESELLSCHAFT, of Frankfurt am Main, Federal Republic of Germany, a company of the Federal Republic of Germany
- [22] Filed: June 2, 1987
- [21] Application Serial No: 35356

FOREIGN APPLICATION PRIORITY DATA

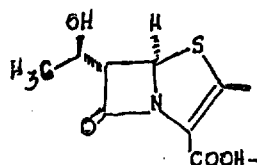
- [31] Number (s) : P 36 18813.1
- [32] Date (s) : June 4, 1986
- [38] Country (ies) : Federal Republic of Germany
- [52] PH Class 514/195
- [51] Int. Class A61K 31/43; A61K 31/545
- [58] Field of Search 514/195
- [56] Reference (s) Cited and/or Considered: None

57] A B S T R A C T

A pharmaceutical formulation having a synergistic anti-bacterial activity and comprising

a) a cephalosporin derivative or a physiologically acceptable salt or ester thereof and

b) a penem antibiotic of the basic structure (3)



or a physiologically acceptable salt or ester thereof, a process for preparing such a formulation and its use for the treatment of bacterial infections.

