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<p>(54) Title: N<sup>1</sup>-MODIFIED GLYCOPEPTIDES</p> <p>(57) Abstract</p> <p>The present invention is directed to N<sup>1</sup>-acylated derivatives of desleucylA82846B. These derivatives are useful as antibacterials.</p>		

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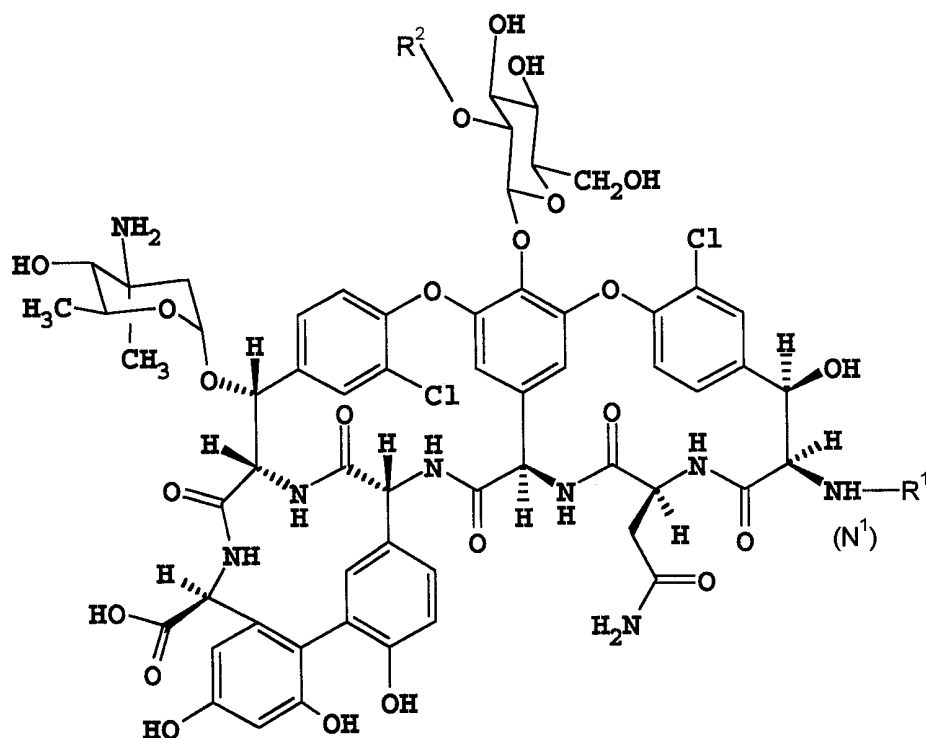
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**N<sup>1</sup>-MODIFIED GLYCOPEPTIDES**

The present invention is directed to glycopeptides and is directed in particular to modifications of A82846B and its N<sup>DISACC</sup> variations. In the claimed compounds, the original N<sup>1</sup> amino acid, N-methyl-D-leucine, has been removed and replaced with an acyl group or with an acyl group derived from an alternate  $\alpha$ -amino acid.

10 The present invention is directed to compounds of the formula



I

wherein R<sup>1</sup> represents

15 alkanoyl of C<sub>2</sub>-C<sub>10</sub> which is unsubstituted, or which is substituted by a phenyl, or which is substituted on other than the  $\alpha$ -carbon atom by an amino or protected amino group; benzoyl or substituted benzoyl bearing one or two substituents each of which is independently halo, loweralkyl of C<sub>1</sub>-C<sub>4</sub>, loweralkoxy of C<sub>1</sub>-C<sub>4</sub> or phenyl;

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an acyl derived from an  $\alpha$ -amino acid or an acyl derived from a protected  $\alpha$ -amino acid, said  $\alpha$ -amino acid being selected from the group consisting of:

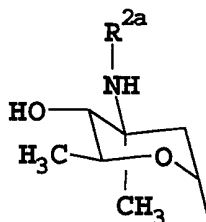
alanine,  
5 arginine,  
asparagine,  
aspartic acid,  
cysteine,  
glutamic acid,  
10 glutamine,  
glycine,  
histidine,  
isoleucine,  
leucine,  
15 lysine,  
methionine,  
3-phenylalanine,  
3-(p-chlorophenyl) alanine,  
proline,  
20 serine,  
threonine,  
tryptophan and  
valine,

in either D- or L-form; or

25 an acyl derived from an  $\alpha$ -amino acid as defined above which bears on the amine a substituent which is alkyl of C<sub>1</sub>-C<sub>10</sub>, benzyl, phenylbenzyl, or p-chlorobenzyl, with the proviso that the acyl derived from N-methyl-D-leucine is excluded;

30 R<sup>2</sup> represents hydrogen, or epivancosaminyl of the formula

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Wherein  $R^{2a}$  represents hydrogen or  $-\text{CH}_2-\text{R}^3$ ; and  $R^3$  represents hydrogen,

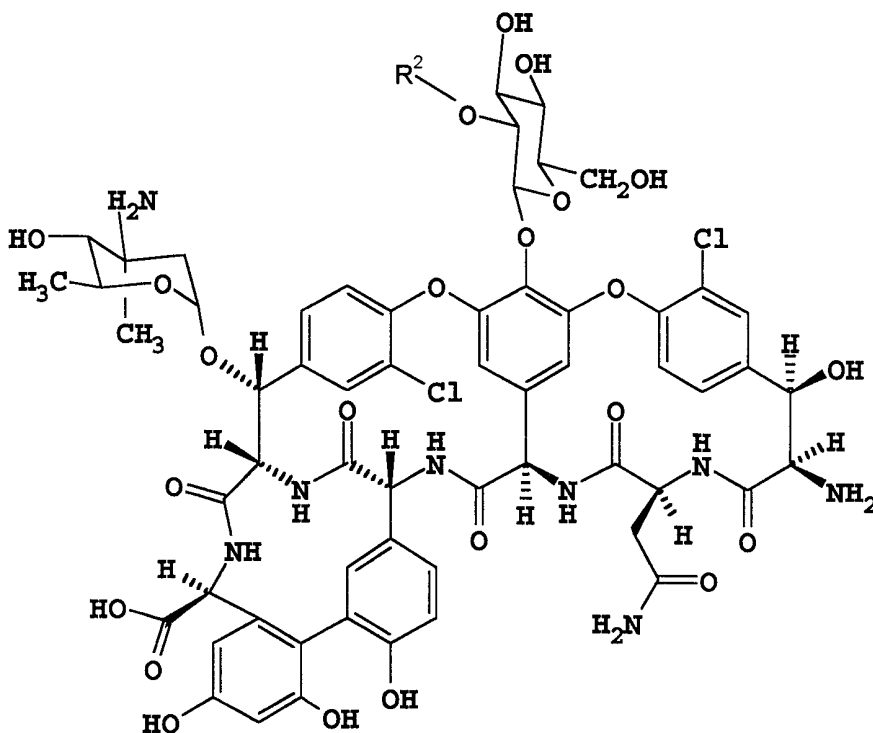
- 5       alkyl of  $\text{C}_1-\text{C}_{11}$ ,  
        alkyl of  $\text{C}_1-\text{C}_{11}-\text{R}^4$ , or  
         $\text{R}^4 - (\text{linker})_{(0 \text{ or } 1)}-\text{R}^4$  or 1,

wherein each  $\text{R}^4$  is independently phenyl or phenyl substituted by one or two substituents, each of which is  
 10       independently halo, loweralkyl of  $\text{C}_1-\text{C}_8$ , loweralkoxy of  $\text{C}_1-\text{C}_8$ , loweralkylthio of  $\text{C}_1-\text{C}_4$ , or trifluoromethyl, and  
        "linker" is  $-\text{O}-$ ,  $-\text{CH}_2-$ , or  $-\text{O}-(\text{CH}_2)_n-$  wherein  $n$  is 1-3;  
        and the pharmaceutically acceptable salts thereof.

When  $\text{R}^1$  represents alkanoyl of  $\text{C}_2-\text{C}_{10}$ , it can be a  
 15       straight-chain alkanoyl, or it can be an alkanoyl which is branched to any degree. Likewise, when  $\text{R}^3$  represents alkyl of  $\text{C}_1-\text{C}_{11}$ , it can be straight-chain or branched.

The compounds of the present invention are prepared from the corresponding "A82846B hexapeptides" of the  
 20       formula:

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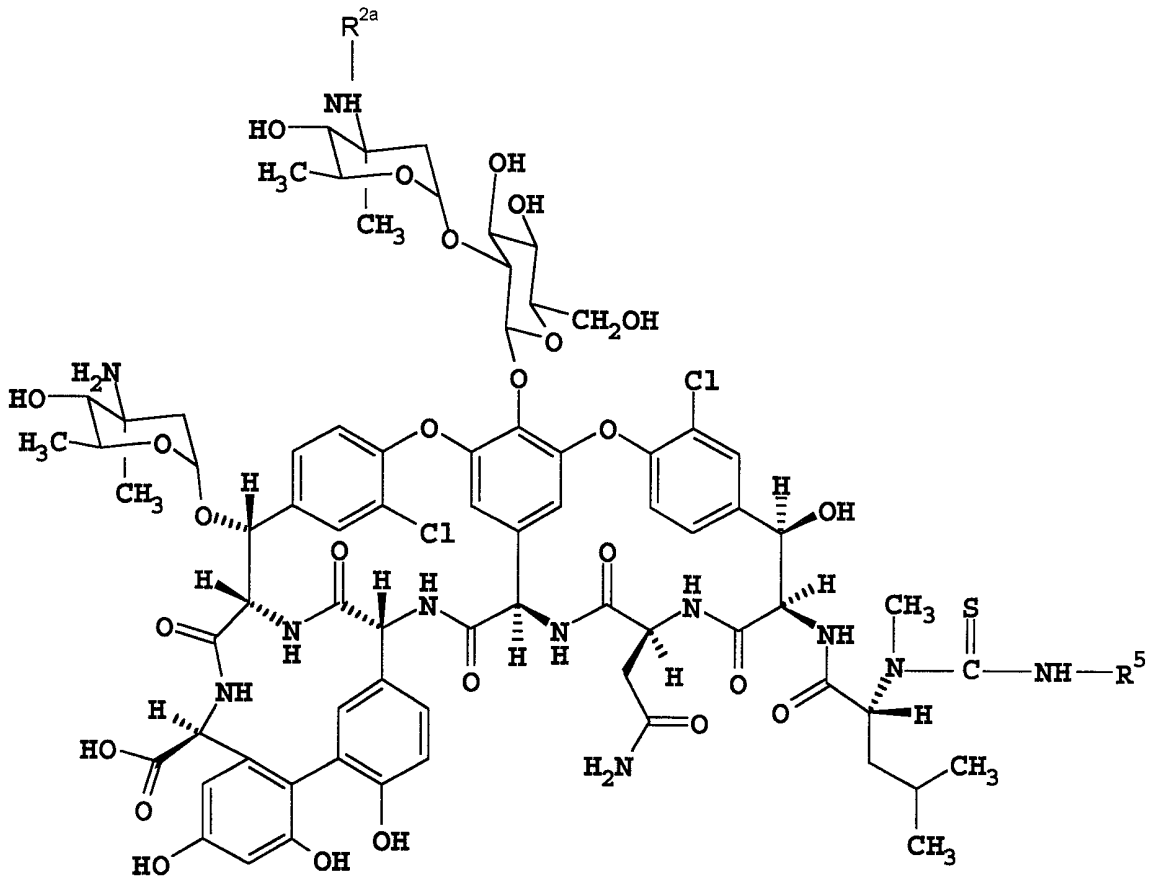
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wherein  $R^2$  is as defined above. These "A82846B  
 hexapeptides" are so called because the normal  $N^1$  amino acid  
 5 N-methyl-D-leucine, has been removed, reducing the number of  
 amino acids in the parent glycopeptide from seven to six.

The compounds of the present invention are prepared by  
 reacting an A82846B hexapeptide with an activated ester of  
 an alkanolic acid of the desired acyl group  $R^1$ . By  
 10 "activated ester" is meant an ester which renders the  
 carboxyl function more reactive to coupling with the amine  
 of the A82846B hexapeptide. The reaction of the A82846B  
 hexapeptide and activated ester is carried out in an organic  
 solvent, suitably a polar solvent such as dimethylformamide,  
 15 dimethyl sulfoxide, or a mixture of dimethylformamide and  
 dimethyl sulfoxide. The reaction proceeds under  
 temperatures of a wide range, such as  $25^\circ$  to  $100^\circ$  C., but is



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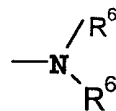
In the foregoing formula, R<sup>5</sup> represents

alkyl of C<sub>1</sub>-C<sub>10</sub>,

5 phenyl,

naphthyl, or

phenyl substituted by one or two substituents, each of which is independently halo, loweralkyl of C<sub>1</sub>-C<sub>4</sub>, loweralkoxy of C<sub>1</sub>-C<sub>4</sub>, benzyloxy, nitro, or



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wherein each R<sup>6</sup> is independently loweralkyl of C<sub>1</sub>-C<sub>4</sub>.

This reaction is conveniently carried out in water with pyridine, at a temperature of 25°-30°C, employing a slight excess of the isothiocyanate reactant. The N<sup>LEU</sup>-

15 (thiocarbamoyl)A82846B intermediate can be separated in conventional manner or can be employed after removal of

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reaction solvent in the second step of the Edman degradation.

In the second step, the N<sup>LEU</sup>-(thiocarbamoyl)A82846B is reacted with an organic acid, preferably trifluoroacetic acid, in a non-polar solvent such as dichloromethane. The reaction proceeds at temperatures of from 0°C to 35°C but is preferably carried out at temperatures of from 0°C to 25°C. The reaction is generally complete in several hours. The resulting hexapeptide product is separated and purified if desired in conventional procedures.

The second step of the Edman degradation can in some instances result in loss of the disaccharide epivancosamine. Longer reaction times can be used to obtain the des-epivancosaminyl compound (R<sup>2</sup>=hydrogen).

Other variations at the disaccharide position of the molecule can be obtained in conventional procedures. As described above, the Edman degradation and subsequent acylation can be carried out with the naturally-occurring disaccharide (R<sup>2</sup>=epivancosaminyl with R<sup>2a</sup>=H) or with a disaccharide derivative (R<sup>2</sup>=epivancosaminyl with R<sup>2a</sup>=CH<sub>2</sub>-R<sup>3</sup>). This approach to synthesis of the present compounds is illustrated by the preparations below of Examples 12 and 26. However, it is also possible to prepare those claimed compounds with a disaccharide derivative (R<sup>2</sup>=epivancosaminyl with R<sup>2a</sup>=-CH<sub>2</sub>-R<sup>3</sup>) by first conducting the Edman degradation

and subsequent acylation on A82846B, with its naturally occurring R<sup>2</sup>=epivancosaminy1, and thereafter introducing the desired epivancosaminy1 substituent -CH<sub>2</sub>-R<sup>3</sup>. This is illustrated by Examples 34 and 35.

5           Whether the -CH<sub>2</sub>-R<sup>3</sup> substituent is introduced prior to Edman degradation and acylation, or after, the same conventional process is used. In this process, the substrate compound is reductively alkylated with the aldehyde suitable to introduce the desired -CH<sub>2</sub>-R<sup>3</sup> group.  
10 This process is taught in various references, see U.S. 5,591,714, and EPO 667,353.

The compounds of the present invention readily form salts, which can be prepared in conventional manner.

15           The following examples illustrate the preparation of the compounds of the present invention.

**Preparation of N<sup>LEU</sup>-(phenylthiocarbamoyl)-N<sup>DISACC</sup>-**

**(p-(p-chlorophenyl)benzyl)A82846B**

N<sup>DISACC</sup>-(p-(p-Chlorophenyl)benzyl)A82846B  
20 trihydrochloride (100.0 mg, 0.0526 mmol) was dissolved in 10 ml H<sub>2</sub>O - pyridine (1:1 v/v) and treated with phenyl isothiocyanate (0.010 ml, 0.083 mmol). The resulting mixture was stirred at room temperature for 1 hr at which time HPLC analysis indicated complete consumption of the  
25 starting material. The reaction mixture was concentrated *in vacuo* and the crude product was purified by preparative HPLC to give 76.6 mg (76% yield) of the title compound. FAB-MS: calc. for C<sub>93</sub>H<sub>102</sub>Cl<sub>3</sub>N<sub>11</sub>O<sub>26</sub>S 1925.5, obtained 1928.5 (M+3).

**Preparation of N<sup>DISACC</sup>-(p-(p-chlorophenyl)benzyl)-  
desleucylA82846B**

5 **from isolated thiourea**

A sample of the purified N<sup>LEU</sup>-(phenylthiocarbamoyl)-  
N<sup>DISACC</sup>-(p-(p-chlorophenyl)benzyl)A82846B (63.3 mg, 0.0327  
mmol) was suspended in 10 ml CH<sub>2</sub>Cl<sub>2</sub>, cooled to 0 °C, then  
treated with trifluoroacetic acid (0.10 ml). After 1 hr the  
10 reaction mixture was warmed to room temperature and stirred  
an additional 2 hr. The solvent was removed *in vacuo* and  
the crude product was purified by preparative HPLC to give  
25.3 mg (46% yield) of the title compound as a white powder.  
FAB-MS: calc. for C<sub>79</sub>H<sub>84</sub>Cl<sub>3</sub>N<sub>9</sub>O<sub>25</sub> 1663.5, obtained 1666.4  
15 (M+3).

**Preparation of N<sup>DISACC</sup>-(p-phenylbenzyl)desleucylA82846B  
without isolation of thiourea intermediate**

N<sup>DISACC</sup>-(p-Phenylbenzyl)A82846B (41.0 mg, 0.0233 mmol)  
20 was dissolved in 4 ml H<sub>2</sub>O - pyridine (1:1 v/v) and treated  
with phenyl isothiocyanate (0.0040 ml, 0.033 mmol). The  
resulting mixture was stirred at room temperature for 3 hr  
at which time HPLC analysis indicated complete consumption  
of the starting material. The reaction mixture was  
25 concentrated *in vacuo* to give the crude thiourea  
intermediate as a white solid. The thiourea derivative was  
then suspended in 10 ml CH<sub>2</sub>Cl<sub>2</sub>, cooled to 0 °C, then treated  
with trifluoroacetic acid (0.25 ml). After 30 minutes the  
reaction mixture was warmed to room temperature and stirred  
30 an additional 1 hr. The solvent was removed *in vacuo* and

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the crude product was purified by preparative HPLC to give 14.0 mg (37% yield) of the title compound as a white powder. FAB-MS: calc. for  $C_{79}H_{85}Cl_2N_9O_{25}$  1629.5, obtained 1632.5 (M+3).

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#### Preparation of Example 1

A sample of desleucylA82846B (101 mg, 0.0689 mmol) and the hydroxybenzotriazole hydrate active ester of 4-phenylbenzoic acid (47 mg, 0.149 mmol) was dissolved in 10 ml DMF. The resulting mixture was stirred at room temperature for 2 hours at which time HPLC analysis revealed complete consumption of the starting material. The reaction mixture was concentrated *in vacuo* and the crude product was purified by preparative HPLC to give 14 mg (12% yield) of  $N^1$ -(p-phenylbenzoyl)desleucylA82846B.

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#### Preparation of Example 26

A sample of  $N^{DISACC}$ -(p-phenylbenzyl)desleucylA82846B (140 mg, 0.0858 mmol) and the hydroxybenzotriazole hydrate active ester of N-BOC-D-proline (66 mg, 0.199 mmol) was dissolved in 12 ml DMF. The resulting mixture was stirred at room temperature for 1 hour at which time HPLC analysis revealed consumption of the starting material. The reaction mixture was concentrated *in vacuo* and the crude product purified by preparative HPLC to give 77.5 mg (49% yield) of  $N^1$ -(N-BOC-D-proline) derivative of  $N^{DISACC}$ -(p-phenylbenzyl)desleucylA82846B.

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#### Preparation of Example 12

A sample of purified  $N^1$ -(N-BOC-D-proline) derivative of  $N^{DISACC}$ -(p-phenylbenzyl)desleucylA82846B (52.5 mg, 0.0287

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mmol) was suspended in 9 ml CH<sub>2</sub>Cl<sub>2</sub>, cooled to 0° C, then treated with trifluoroacetic acid (0.5 ml). After 10 minutes the reaction mixture was warmed to room temperature and stirred for an additional 50 minutes. HPLC analysis revealed complete consumption of the starting material. The solvent was removed *in vacuo*, and the crude product was purified by preparative HPLC to give 15 mg (30% yield) of N<sup>1</sup>-D-proline derivative of N<sup>DISACC</sup>-(p-phenylbenzyl)desleucylA82846B.

10

#### Preparation of Examples 34 and 35

A sample of N<sup>1</sup>-D-leucine derivative of desleucylA82846B (95 mg, 0.0602 mmol) and p-phenylbenzaldehyde (14 mg, 0.0768 mmol) was dissolved in 10 ml N,N-dimethylformamide (DMF) and 10 ml methanol (MeOH). The resulting mixture was heated to 75°C and stirred for 1 hour 15 minutes. At this time, sodium cyanoborohydride (26 mg, 0.413 mmol) was added and the reaction stirred at 75°C for another 1 hour 30 minutes at which time HPLC analysis revealed consumption of the starting material. The reaction mixture was concentrated *in vacuo* and the crude product purified by preparative HPLC to give 32 mg (30%) of N<sup>1</sup>-(N-p-phenylbenzyl)-D-leucine derivative of desleucylA82846B and 3 mg (2.6%) of N<sup>DISACC</sup>-(p-phenylbenzyl)-N<sup>1</sup>-(N-p-phenylbenzyl)-D-leucine derivative of desleucylA82846B.

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The HPLC procedures reported in these examples were as follows:

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Analytical: Reactions were monitored by analytical HPLC using a Waters C<sub>18</sub>  $\mu$ Bondapak or Novapak C<sub>18</sub> column (3.9x300 mm) and UV detection at 280 nm. Elution was accomplished with a linear gradient of 5% CH<sub>3</sub>CN - 95% buffer to 80% CH<sub>3</sub>CN - 20% buffer over 30 minutes. The buffer used was 0.5% triethylamine in water, adjusted to pH 3 with H<sub>3</sub>PO<sub>4</sub>.

Preparative: Crude reaction mixtures were purified by preparative HPLC using a Waters C<sub>18</sub> Nova-Pak column (40x300 mm) and UV detection at 280 nm. Elution was accomplished with a linear gradient of 5% CH<sub>3</sub>CN - 95% buffer to 80% CH<sub>3</sub>CN - 20% buffer over 30 minutes. The buffer used was 0.5% triethylamine in water, adjusted to pH 3 with H<sub>3</sub>PO<sub>4</sub>. The desired fractions were subsequently desalted with a Waters C<sub>18</sub> Sep-Pak (35 cc) followed by lyophilization.

Compounds were desalted as follows. A Waters Sep-Pak cartridge was pre-wet with methanol (2-3 column volumes) then conditioned with water (2-3 column volumes). The sample, dissolved in a minimum volume of water, was loaded onto the Sep-Pak column which was then washed with water (2-3 column volumes) to remove the unwanted salts. The product was then eluted with an appropriate solvent system, typically 1:1 CH<sub>3</sub>CN/H<sub>2</sub>O, CH<sub>3</sub>CN, and/or methanol. The organic solvent component was removed *in vacuo* and the resulting aqueous solution lyophilized to give the final product.

Representative compounds of the present invention are listed in the following tables:

TABLE I: SIMPLE ACYL DERIVATIVES

Example #	FAB-MS	M + X	HPLC, min	Compound Name
1	1644.2	1	14.7	N <sup>1</sup> - (p-phenylbenzoyl) desleucylA82846B
2	1667.4	2	17.3	N <sup>1</sup> - (8-phenyl-n-octanoyl) desleucylA82846B
3	1834.7	3	20.4	N <sup>1</sup> - (8-phenyl-n-octanoyl) -N <sup>D</sup> ISACC - (p-phenylbenzyl) desleucylA82846B
4	1564.4	3	11.0	N <sup>1</sup> - (4-methyl-n-pentanoyl) desleucylA82846B
5	1730.4	3	17.3	N <sup>1</sup> - (4-methyl-n-pentanoyl) -N <sup>D</sup> ISACC - (p-phenylbenzyl) desleucylA82846B
6	1812.7	3	18.9	N <sup>1</sup> - (p-phenylbenzoyl) -N <sup>D</sup> ISACC - (p-phenylbenzyl) desleucylA82846B
7	1764.4	0	18.7	N <sup>1</sup> - (4-methyl-n-pentanoyl) -N <sup>D</sup> ISACC - [p- (p-chlorophenyl) benzyl] desleucylA82846B
8	1868.5	3	23.0	N <sup>1</sup> - (8-phenyl-n-octanoyl) -N <sup>D</sup> ISACC - [p- (p-chlorophenyl) benzyl] desleucylA82846B
9	1892.9	2	21.1	N <sup>1</sup> - [7- (tert-butoxycarbonylo) -n-heptanoyl] -N <sup>D</sup> ISACC - [p- (p-chlorophenyl) benzyl] desleucylA82846B
10	1793.5	3	14.9	N <sup>1</sup> - (7-amino-n-heptanoyl) -N <sup>D</sup> ISACC - [p- (p-chlorophenyl) benzyl] desleucylA82846B

TABLE II: AMINO ACID DERIVATIVES

Example #	FAB-MS	M + X	HPLC, min	Compound Name
11	1845.5	3	18.3	N <sup>1</sup> - (N-BOC-L-leucine) derivative of N <sup>DISACC</sup> - (p-phenylbenzyl)desleucylA82846B
12	1729.3	3	14.2	N <sup>1</sup> -D-proline derivative of N <sup>DISACC</sup> - (p-phenylbenzyl)desleucylA82846B
13	1745.4	3	14.2	N <sup>1</sup> -D-leucine derivative of N <sup>DISACC</sup> - (p-phenylbenzyl)desleucylA82846B
14	1679.6	3	13.3	N <sup>1</sup> - (N-BOC-D-leucine) derivative of desleucylA82846B
15	1863.3	3	18.0	N <sup>1</sup> - (N-BOC-D-methionine) derivative of N <sup>DISACC</sup> - (p-phenylbenzyl)desleucylA82846B
16	1794.7	3	14.9	N <sup>1</sup> - (N,N'-DIBOC-D-lysine) derivative of desleucylA82846B
17	1579.2	3	8.5	N <sup>1</sup> -D-leucine derivative of desleucylA82846B
18	1845.5	3	18.3	N <sup>1</sup> - (N-BOC-D-leucine) derivative of N <sup>DISACC</sup> - (p-phenylbenzyl)desleucylA82846B
19	1960.4	3	19.2	N <sup>1</sup> - (N,N'-DIBOC-D-lysine) derivative of N <sup>DISACC</sup> - (p-phenylbenzyl)desleucylA82846B
20	1747.2	3	15.6	N <sup>1</sup> - [N-BOC-D-3- (p-chlorophenyl) alanine] derivative of desleucylA82846B
21	1913.5	3	19.6	N <sup>1</sup> - [N-BOC-D-3- (p-chlorophenyl) alanine] derivative of N <sup>DISACC</sup> - (p-phenylbenzyl)desleucylA82846B
22	1813.5	3	14.4	N <sup>1</sup> - [D-3- (p-chlorophenyl) alanine] derivative of N <sup>DISACC</sup> - (p-phenylbenzyl)desleucylA82846B

TABLE II (continued)

Example #	FAB-MS	M + X	HPLC, min	Compound Name
23	1760.4	3	12.9	N <sup>1</sup> -D-lysine derivative of N <sup>DISACC</sup> -(p-phenylbenzyl)desleucylA82846B
24	1663.1	3	11.6	N <sup>1</sup> -(N-BOC-D-proline) derivative of desleucylA82846B
25	1919.3	4	18.7	N <sup>1</sup> -(N-BOC-D-tryptophan) derivative of N <sup>DISACC</sup> -(p-phenylbenzyl)desleucylA82846B
26	1830.1	3	17.7	N <sup>1</sup> -(N-BOC-D-proline) derivative of N <sup>DISACC</sup> -(p-phenylbenzyl)desleucylA82846B
27	1745.2	3	15.1	N <sup>1</sup> -L-leucine derivative of N <sup>DISACC</sup> -(p-phenylbenzyl)desleucylA82846B
28	1913.4	3	19.4	N <sup>1</sup> -(N-BOC-L-3-(p-chlorophenyl)alanine) derivative of N <sup>DISACC</sup> -(p-phenylbenzyl)desleucylA82846B
29	1829.5	3	17.1	N <sup>1</sup> -(N-BOC-L-proline) derivative of N <sup>DISACC</sup> -(p-phenylbenzyl)desleucylA82846B
30	1960.5	3	19.1	N <sup>1</sup> -(N,N'-DIBOC-L-lysine) derivative of N <sup>DISACC</sup> -(p-phenylbenzyl)desleucylA82846B
31	1760.4	3	13.3	N <sup>1</sup> -L-lysine derivative of N <sup>DISACC</sup> -(p-phenylbenzyl)desleucylA82846B
32	1729.4	3	14.3	N <sup>1</sup> -L-proline derivative of N <sup>DISACC</sup> -(p-phenylbenzyl)desleucylA82846B
33	1813.3	3	16.2	N <sup>1</sup> -[L-3-(p-chlorophenyl)alanine] derivative of N <sup>DISACC</sup> -(p-phenylbenzyl)desleucylA82846B

TABLE II (Continued)

Example #	FAB-MS	M + X	HPLC, min	Compound Name
34	1745.4	3	13.3	N <sup>1</sup> -[N-(p-phenylbenzyl)-D-leucine] derivative of desleucylA82846B
35	1911.6	3	17.9	N <sup>1</sup> -[N-(p-phenylbenzyl)-D-leucine] derivative of N <sup>DISACC</sup> -(p-phenylbenzyl) desleucylA82846B
36	1536.5	3	16.5	N <sup>1</sup> -(N-BOC-D-leucine) derivative of desepivancosaminyldesleucylA82846B
37	1436.3	3	9.1	N <sup>1</sup> -D-leucine derivative of desepivancosaminyldesleucylA82846B
38	1747.4	3	14.5	N <sup>1</sup> -(N-n-hexyl-D-leucine) derivative of N <sup>DISACC</sup> -n-hexyl desleucylA82846B
39	1661.7	1	11.0	N <sup>1</sup> -(N-n-hexyl-D-leucine) derivative of desleucylA82846B
40	1727.3	3	14.8	N <sup>1</sup> -(N-BOC-N-methyl-D-phenylalanine) derivative of desleucylA82846B
41	1679.2	3	14.1	N <sup>1</sup> -(N-BOC-N-methyl-D-valine) derivative of desleucylA82846B
42	1577.3	1	7.7	N <sup>1</sup> -(N-methyl-D-valine) derivative of desleucylA82846B

The compounds of the present invention are useful for the treatment of bacterial infections. Therefore, in another embodiment, the present invention is directed to a method for controlling a bacterial infection in a host animal, typically a warm-blooded animal, which comprises administering to the host animal an effective, antibacterial amount of a compound of the present invention. In this embodiment, the compounds can be used to control and treat infections due to various bacteria, but especially gram-positive bacteria. In a preferred embodiment, the compounds are used to control and treat infections due to bacteria resistant to existing antibacterials. For example, certain bacteria are resistant to methicillin, and yet others are resistant to vancomycin and/or teicoplanin. The present compounds provide a technique for controlling and treating infections due to such resistant bacterial species.

In carrying out this embodiment of the invention, the compounds of the present invention can be administered by any of the conventional techniques, including the oral route and parenteral routes such as intravenous and intramuscular. The amount of compound to be employed is not critical and will vary depending on the particular compound employed, the route of administration, the severity of the infection, the interval between dosings, and other factors known to those skilled in the art. In general, a dose of from about 0.5 to about 100 mg/kg will be effective; and in many situations, lesser doses of from about 0.5 to about 50 mg/kg will be effective. A compound of the present invention can be administered in a single dose, but in the known manner of

antibacterial therapy, a compound of the present invention is typically administered repeatedly over a period of time, such as a matter of days or weeks, to ensure control of the bacterial infection.

5           Also in accordance with known antibacterial therapy, a compound of the present invention is typically formulated for convenient delivery of the requisite dose. Therefore, in another embodiment, the present invention is directed to a pharmaceutical formulation comprising a compound of the  
10 present invention, in combination with a pharmaceutically-acceptable carrier. Such carriers are well known for both oral and parenteral routes of delivery. In general, a formulation will comprise a compound of the present  
15 invention in a concentration of from about 0.1 to about 90% by weight, and often from about 1.0 to about 3%.

The antibacterial efficacy of the present compounds is illustrated by Table III. The minimal inhibitory concentrations (MICs) were determined using a standard broth micro-dilution assay.



TABLE IV: ACTIVITY OF AMINO ACID DERIVATIVES\*

Example #	Resistant	Sensitive	SA 446	SA 489	SA 447	SA X400	SA X778	SA 491	SA S13E	SA 1199
11	45	1.7	1	2	1	1	0.5	2	1	1
12	2.8	0.19	2	2	0.5	1	0.25	0.5	2	1
13	2.4	0.095	1	0.5	1	0.5	1	1	0.5	1
14	>128	6.1								
15	27	1.2	1	1	1	1	0.5	1	1	2
16	>128	7								
17	>32	0.5	0.5	0.06	0.5	0.06	0.06	0.125	0.25	0.25
18	27	0.87	0.5	0.125	0.5	0.25	0.25	≤.06	0.5	0.5
19	64	2.6	2	1	2	2	2	1	2	2
20	>128	2	0.5	≤.06	0.25	≤.06	0.25	≤.06	0.125	0.125
21	11	1.5	0.5	0.25	0.5	0.5	0.5	0.5	0.5	0.5

Example #	SA 1199A	SH 105	SH 415	SE 270	EF 180	EF 180-1	EF 2041	EF 276	EG 245	HFRD	EC 14
11	1	0.5	1	0.5	8	0.25	1	2	1	>64	>64
12	0.25	0.125	0.25	0.125	1	≤.06	0.25	1	0.25	32	>64
13	0.25	1	0.5	0.25	0.25	≤.06	≤.06	0.5	≤.06	16	>64
14											
15	0.125	1	1	0.25	8	≤.06	0.25	0.5	1	>64	>64
16											
17	≤.06	0.5	1	0.25	1	≤.06	≤.06	0.06	0.06	32	>64
18	no growth	1	1	0.25	2	0.5	≤.06	0.5	1	16	>64
19	no growth	4	4	2	8	1	0.5	2	2	>64	>64
20	no growth	8	16	0.125	16	0.25	≤.06	0.125	0.5	8	>64
21	no growth	2	2	0.5	1	0.5	0.5	1	1	2	>64

TABLE IV (continued)

Example #	Resistant	Sensitive	SA 446	SA 489	SA 447	SA X400	SA X778	SA 491	SA S13E	SA 1199
22	6.7	0.66	1	1	1	0.5	1	0.5	2	2
23	2	0.29	1	0.5	1	2	2	0.5	2	0.5
24	>128	4	4	2	4	2	1	1	2	2
25	27	1.3	4	1	2	2	2	2	2	1
26	23	0.76	2	0.5	1	0.5	0.5	≤.06	1	1
27	16	1	2	4	1	2	1	1	2	1
28	13	1.7	4	1	2	2	1	2	2	2
29	27	1.2	2	0.25	0.5	0.25	0.125	≤.06	0.5	0.125
30	38	2.3	8	1	2	2	1	2	2	2
31	5.6	0.33	0.5	2	2	2	0.5	0.5	1	0.5

Example #	SA 1199A	SH 105	SH 415	SE 270	EF 180	EF 180-1	EF 2041	EF 276	EG 245	HFRD	EC 14
22	0.25	2	4	0.25	2	≤.06	1	1	0.25	>64	>64
23	0.25	1	1	0.125	0.5	≤.06	0.5	0.25	0.125	>64	>64
24	1	16	32	2	>64	1	1	1	8	>64	>64
25	0.5	2	4	2	8	≤.06	1	2	2	>64	>64
26	0.125	1	2	0.25	4	≤.06	0.25	1	0.5	>64	>64
27	0.5	0.125	2	0.25	4	0.25	1	1	0.5	64	>64
28	1	2	4	1	2	0.5	2	1	2	>64	>64
29	≤.06	0.125	0.5	≤.06	4	≤.06	0.125	0.25	2	>64	>64
30	1	2	2	1	8	0.5	1	2	2	>64	>64
31	0.25	0.5	2	0.5	1	0.25	1	2	0.5	>64	>64

TABLE IV (continued)

Example #	Resistant	Sensitive	SA 446	SA 489	SA 447	SA X400	SA X778	SA 491	SA S13E	SA 1199
32	16	0.76	1	1	1	2	0.5	0.125	0.25	0.25
33	27	2.6	1	2	1	1	1	0.5	1	0.5
34	38	0.44	0.125	≤.06	0.125	≤.06	≤.06	≤.06	≤.06	0.125
35	4.8	0.66	2	2	2	2	1	1	2	2
36	>128	16	8	4	16	4	4	2	4	4
37	>32	0.87	0.5	0.25	1	0.25	0.25	0.5	0.25	0.5
38	6.7	0.19	1	0.25	1	1	0.5	≤.06	0.5	1
39	45	0.38	≤.06	≤.06	0.5	≤.06	≤.06	≤.06	0.125	0.125
40	>128	9.2	4	4	8	4	4	2	4	4
41	>128	84	32	16	32	16	8	4	16	16
42	128	0.66	0.5	0.5	0.5	0.5	2	1	1	1

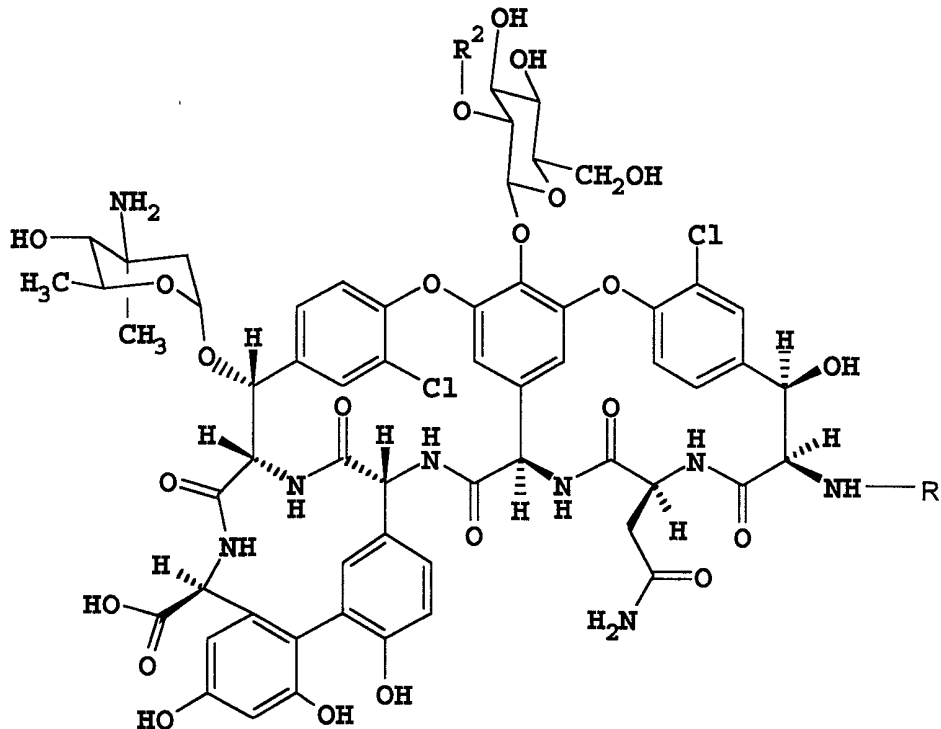
  

Example #	SA 1199A	SH 105	SH 415	SE 270	EF 180	EF 180-1	EF 2041	EF 276	EG 245	HFRD	EC 14
32	≤.06	0.125	0.5	0.125	2	0.125	1	2	0.5	>64	>64
33	0.25	0.5	0.5	0.25	4	0.5	2	4	1	>64	>64
34	≤.06	≤.06	4	0.25	2	≤.06	0.25	≤.06	≤.06	64	>64
35	1	0.5	2	1	1	0.25	0.5	1	1	>64	>64
36	4	2	>64	16	>64	4	8	4	16	>64	>64
37	0.125	0.25	4	0.5	>64	0.25	0.5	0.25	0.5	64	>64
38	≤.06	1	1	1	2	no growth	≤.06	0.25	0.5	no growth	>64
39	≤.06	0.5	2	0.25	2	no growth	≤.06	≤.06	0.5	no growth	>64
40	2	4	64	4	>64	4	2	1	16	>64	>64
41	8	16	64	8	>64	4	8	8	>64	no growth	>64
42		0.5	1	1	64						>64

*Abbreviations	Organism
Resistant	<i>Enterococcus faecium</i> and <i>faecalis</i> (geometric mean of 4-6 isolates)
Sensitive	<i>Enterococcus faecium</i> and <i>faecalis</i> (geometric mean of 4-6 isolates)
SA 446	<i>Staphylococcus aureus</i> 446
SA 489	<i>Staphylococcus aureus</i> 489
SA 447	<i>Staphylococcus aureus</i> 447
SA X400	<i>Staphylococcus aureus</i> X400
SA X778	<i>Staphylococcus aureus</i> X778
SA 491	<i>Staphylococcus aureus</i> 491
SA S13E	<i>Staphylococcus aureus</i> S13E
SA 1199	<i>Staphylococcus aureus</i> SA1199
SA 1199A	<i>Staphylococcus aureus</i> SA1199A
SH 105	<i>Staphylococcus haemolyticus</i> 105
SH 415	<i>Staphylococcus haemolyticus</i> 415
SE 270	<i>Staphylococcus epidermidis</i> 270
EF 180	<i>Enterococcus faecium</i> 180
EF 180-1	<i>Enterococcus faecium</i> 180-1
EF 2041	<i>Enterococcus faecalis</i> 2041
EF 276	<i>Enterococcus faecalis</i> 276
EG 245	<i>Enterococcus gallinarum</i> 245
HFRD	<i>Haemophilus influenzae</i> RD
EC 14	<i>Escherichia coli</i> EC14

WE CLAIM:

1. A compound of the formula



5

wherein  $R^1$  represents

alkanoyl of  $C_2-C_{10}$  which is unsubstituted, or which is substituted by a phenyl, or which is substituted on other than the  $\alpha$ -carbon atom by an amino or protected amino group;

10 benzoyl or substituted benzoyl bearing one or two substituents each of which is independently halo, loweralkyl of  $C_1-C_4$ , loweralkoxy of  $C_1-C_4$  or phenyl;

15 an acyl derived from an  $\alpha$ -amino acid or an acyl derived from a protected  $\alpha$ -amino acid, said  $\alpha$ -amino acid being selected from the group consisting of:

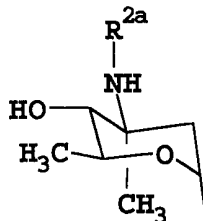
alanine,  
arginine,  
asparagine,  
5 aspartic acid,  
cysteine,  
glutamic acid,  
glutamine,  
glycine,  
10 histidine,  
isoleucine,  
leucine,  
lysine,  
methionine,  
15 3-phenylalanine,  
3-(p-chlorophenyl)alanine,  
proline,  
serine,  
threonine,  
20 tryptophan and  
valine,

in either D- or L-form; or

an acyl derived from an  $\alpha$ -amino acid as defined  
above which bears on the amine a substituent which is alkyl  
25 of C<sub>1</sub>-C<sub>10</sub>, benzyl, phenylbenzyl, or p-chlorobenzyl, with the  
proviso that the acyl derived from N-methyl-D-leucine is  
excluded;

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R<sup>2</sup> represents hydrogen or an epivancosaminyl of the formula



5

wherein R<sup>2a</sup> represents hydrogen or -CH<sub>2</sub>-R<sup>3</sup>; and R<sup>3</sup> represents hydrogen,

alkyl of C<sub>1</sub>-C<sub>11</sub>,

alkyl of C<sub>1</sub>-C<sub>11</sub>-R<sup>4</sup>, or

10 R<sup>4</sup>-(linker<sub>(0 or 1)</sub>-R<sup>4</sup>)<sub>0 or 1</sub>,

wherein each R<sup>4</sup> is independently phenyl or phenyl

substituted by one or two substituents, each of which is independently halo, loweralkyl of C<sub>1</sub>-C<sub>8</sub>, loweralkoxy of C<sub>1</sub>-C<sub>8</sub>, loweralkylthio of C<sub>1</sub>-C<sub>4</sub>, or trifluoromethyl, and

15 "linker" is -O-, -CH<sub>2</sub>-, or -O-(CH<sub>2</sub>)<sub>n</sub>- wherein n is 1-3;

2. A compound of Claim 1 in which R<sup>2</sup> is an epivancosaminyl radical wherein R<sup>2a</sup> represents hydrogen,

3. A compound of Claim 2 in which R<sup>2</sup> is an epivancosaminyl radical wherein R<sup>2a</sup> represents -CH<sub>2</sub>-R<sup>3</sup>.

20 4. A compound of Claim 3 in which R<sup>3</sup> is p-biphenyl.

5. A compound of Claim 3 in which R<sup>3</sup> is p-(p-chlorophenyl)phenyl.



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wherein  $R^2$  is as defined in Claim 1, with an activated ester of an alkanolic acid of the desired  $R^1$  as defined in Claim 1, and if desired, thereafter reductively alkylating the  $N^{DISACC}$  amine and/or forming a pharmaceutically acceptable salt.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/04306

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 38/00

US CL :514/2, 8, 9, 11

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2, 8, 9, 11

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, STN

search terms: A82486?

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,591,714 A (NAGARAJAN et al) 07 January 1997, col.5, lines 20-30.	1-11
X	US 5,312,738 A (HAMILL et al) 17 May 1994, col.2, lines 40-55.	1-11



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*g* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

25 MAY 1999

Date of mailing of the international search report

17 JUN 1999

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