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CHEMICAL ABSTRACTS, vol. 100, 1984, page 583, abstract no. 86115j, Columbus, Ohio, US; A.H. HUNT et al.: "Structure of the pseudoaglycon of actaplanin", & J. ORG. CHEM. 1984, 49(4), 635-40

THE JOURNAL OF ANTIBIOTICS, vol. 38, no. 6, 1985, pages 713-720, Japan Antibiotics Research Association; G.D. ROBERTS et al.: "Structural characterization of glycopeptide antibiotics related to vancomycin by fast atom bombardment mass spectrometry"

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THE JOURNAL OF ANTIBIOTICS, vol. 39, no. 1, 1986, pages 68-75, Japan Antibiotics Research Association; R.D. SITRIN et al.: "Aridicins, novel glycopeptide antibiotics III. Preparation, characterization, and biological activities of aglycone derivatives"

Courier Press, Leamington Spa, England.

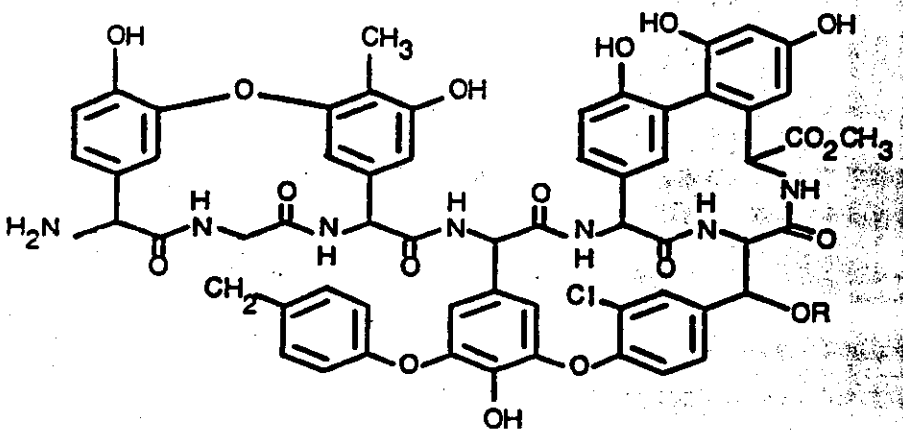
EP 0 132 116 B1

Description

Background of the Invention

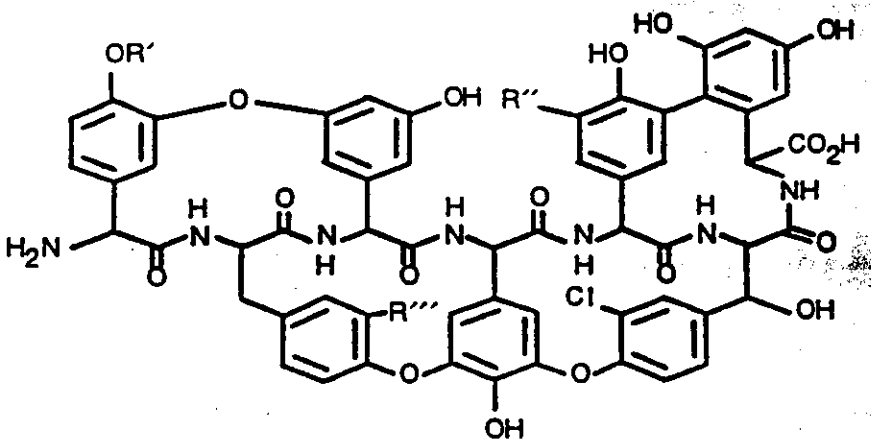
Novel AAD 216 antibiotics of the vancomycin-class are produced by cultivating the new microorganism, *Kibdelosporangium aridium* Shearer, gen. nov., sp. nov. SK&F AAD 216 (ATCC 39323) in aqueous nutrient medium, containing assimilable sources of carbon and nitrogen, under submerged aerobic conditions until a substantial amount of the AAD 216 antibiotic complex is produced and optionally recovering the AAD 216 complex from the culture medium and isolating the individual major antibiotic factors, AAD 216A, AAD 216B, and AAD 216C. The AAD 216 antibiotics and the microorganism, *K. aridium*, are disclosed and claimed in a co-pending European Patent Application (EP—A—132118), Attorney Docket No. SKB 14168 (claiming priority from US Serial No. 513,513 filed July 13, 1983), filed concurrently herewith. A copy of this is enclosed with the documents of the present application and is to form part of the dossier.

European patent application 55069 describes an antibiotic A—4696 pseudo-aglycone, produced by mild acid hydrolysis of the actaplanin antibiotic A—4696 complex, and is of the formula:



wherein R is L-ristosamine.

European patent application 90578 describes A 41030 antibiotics of the formula:



wherein

R' is H, R'' is Cl and R''' is Cl (Factor A);
R' is H, R'' is H and R''' is Cl (Factor B);
R' is Galactose, R'' is Cl and R''' is Cl (Factor C);
R' is H, R'' is H and R''' is H (Factor E); or
R' is Galactosylgalactose, R'' is Cl and R''' is Cl (Factor F).

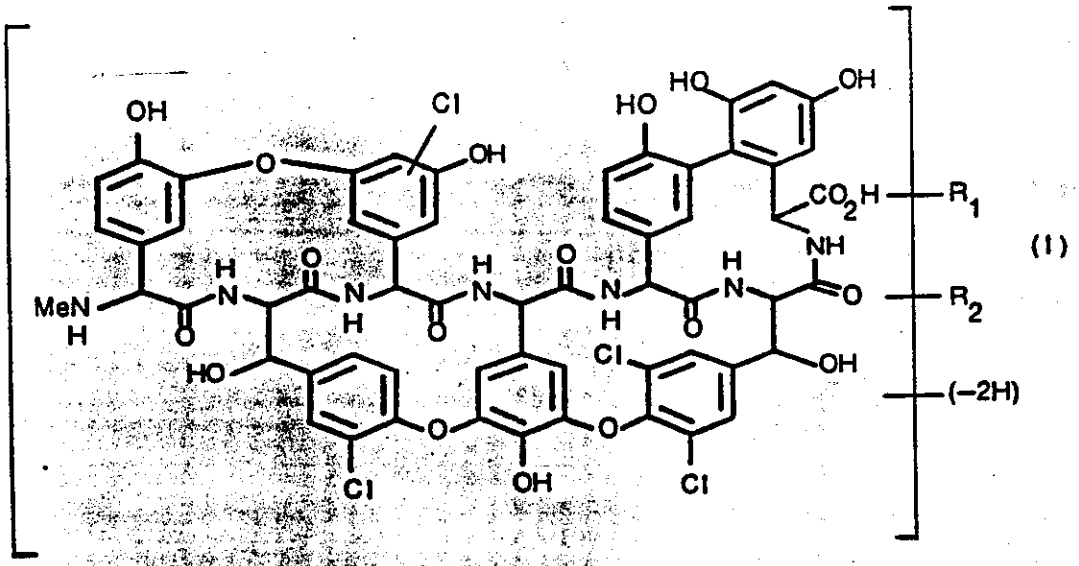
Summary of the Invention

This invention relates to the novel aglycone and pseudo-aglycones of the AAD 216 antibiotics which are prepared by the partial acid hydrolysis of the AAD 216 antibiotics complex or the individual antibiotic factors which comprise the AAD 216 complex followed by chromatographic isolation. The compounds of this invention exhibit antibacterial activity and are useful in animal health applications such as growth promotants and the treatment of bovine mastitis.

Detailed Description of the Invention

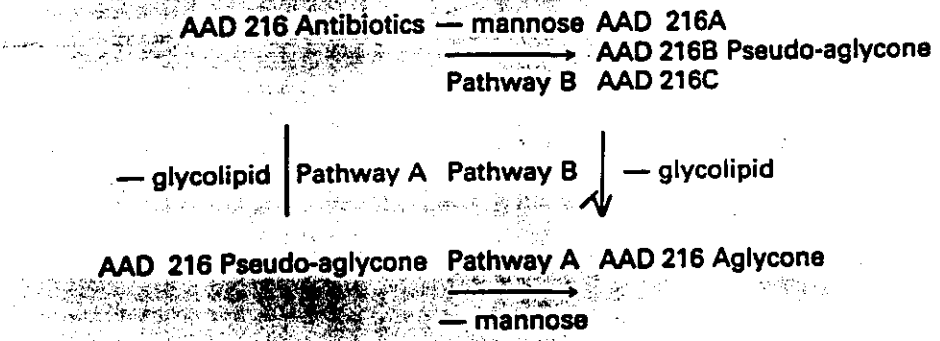
The aglycone and pseudo-aglycones of the instant invention are prepared by the partial acidic

hydrolysis of the AAD 216 antibiotics, which for the purpose of the present application is defined as the AAD 216 antibiotic complex and its major individual antibiotic factors, AAD 216A, AAD 216B and AD 216C. The aglycone and the pseudeo-aglycones of the AAD 216 antibiotics are represented by the following general structural formula (I):



wherein R_1 is hydrogen or a mannosyl radical and R_2 is hydrogen or a glycolipid radical of unknown structure derived from the hydrolyzed AAD 216 antibiotic with the proviso that at least one of R_1 and R_2 is hydrogen. The AAD 216 antibiotic complex is the compound of formula (I) wherein R_1 is mannosyl and R_2 is a glycolipid radical.

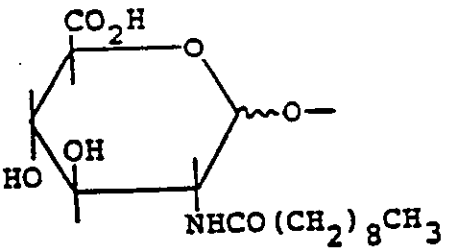
The hydrolysis of the AAD 216 antibiotics proceeds along two pathways to afford the AAD 216 aglycone of the formula (I) wherein R_1 and R_2 are hydrogen as follows:



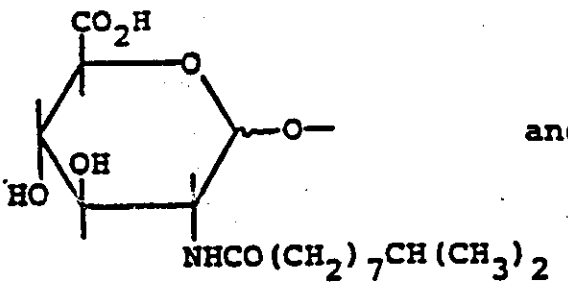
The initial step of the hydrolysis pathway A involves the loss of the glycolipid radicals from the AAD 216 antibiotics to yield the pseudeo-aglycone of formula (I) wherein R_1 is mannosyl and R_2 is hydrogen. This pseudo-aglycone is denominated AAD 216 pseudo-aglycone since it is independent of which AAD 216 antibiotic is hydrolyzed. Subsequent hydrolysis of the AAD 216 pseudo-agylcone yields the AAD 216 aglycone upon the loss of the mannosyl radical.

The initial step of the hydrolysis pathway B involves the loss of the mannosyl radical from the AAD 216 antibiotics to give pseudo-aglycones of the formula (I) wherein R_1 is hydrogen and R_2 is a glycolipid radical of unknown structure which is derived from the AAD 216 antibiotic factor hydrolyzed. Accordingly, these pseudo-aglycones are denominated AAD 216A pseudo-aglycone, AAD 216B pseudo-aglycone or AAD 216C pseudo-aglycone depending on the AAD 216 antibiotic factor hydrolyzed. Where the AAD 216 complex is hydrolyzed, a mixture of these pseudo-aglycones will result.

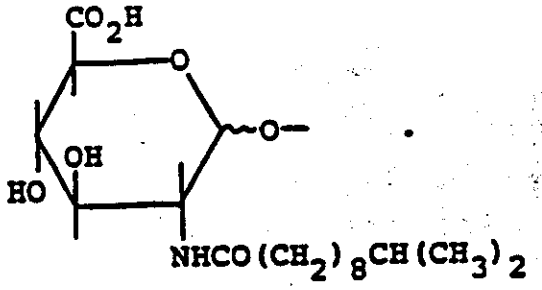
The AAD 216A pseudo-aglycone contains a glycolipid radical of unknown structure with a molecular weight of 330 amu and an empirical formula of $C_{16}H_{28}NO_6$. The methanolysis of AAD 216A pseudo-aglycone produced two major products which were identified as the methylglycosidemethyl ester of an *n*-decanoyldeoxyaminoglycuronic acid and the methylglycoside of either *n*-decanoyldeoxyaminoglycofurano-3,6-lactone or *n*-decanoyldeoxyaminoglycopyrano-3,6-lactose. THe diacetate derivative of first major methanolysis product of AAD 216A pseudo-aglycone was compared with and found to be identical to the diacetate derivative of methyl-2-deoxy-2[(1-oxodecyl)amino]-α-D-glycopyranosiduronic acid methyl ester, which was prepared in a simple two-step process from D-glucosamine. From the above evidence, the structure of the glycolipid radical of AAD 216A pseudo-aglycone is most probably as follows:



Since AAD 216A, AAD 216B and AAD 216C are homologs, the glycolipid radicals of AAD 216B pseudo-aglycone and AAD 216C pseudo-aglycone have molecular weights of 344 and 358, respectively, and empirical formulae of $C_{17}H_{30}NO_6$ and $C_{18}H_{32}NO_6$, respectively. Utilizing comparative studies of the ^{13}C nuclear magnetic resonance spectra of AAD 216A, AAD 216B and AAD 216C as well as a comparative studies of the fatty acid hydrolysis products of the parent antibiotic factors, the glycolipid radicals of AAD 216B pseudo-aglycone and AAD 216C pseudo-aglycone are tenatively assigned the following respective structures:



and



The AAD 216 pseudo-aglycone of the formula (I) wherein R_1 is mannosyl and R_2 is hydrogen has the following characteristics:

(a) pale white-yellow solid which decomposes at 300—350°C;

(b) an empirical formula $C_{65}H_{55}N_7O_{24}Cl_4$;

(c) an approximate elemental composition of 47.54 percent carbon, 4.00 percent hydrogen, 5.89 percent nitrogen and 8.63 percent solution when the water content was 12 percent;

(d) an infrared absorption spectrum in potassium bromide which exhibits peaks at the following wave numbers in cm^{-1}: 3400, 1660, 1610, 1590, 1510, 1460, 1430, 1390, 1300, 1230, 1180, 1150, 1120, 1060, 1010, 970 and 810;

(e) a fast atom bombardment (FAB) mass spectrum with M + H at 1458 (major cluster);

(f) an ultraviolet spectrum in acetonitrile:water (1:1) which exhibits an absorption maximum at 281 nm under acid conditions with an $E_{1\%}$ = 79.7 and at 300 nm under basic conditions with an $E_{1\%}$ = 136;

(g) a carbon magnetic resonance spectrum at 90.56 MHz in $CD_3OD:D_2O$ (1:9) at a pH of 8.7 which exhibits the following chemical shifts in parts per million (ppm) relative to TMS as standard: 177.9, 174.6, 171.7, 170.9, 170.0, 169.2, 162.3, 158.8, 157.9, 155.2, 155.1, 153.9, 151.9, 149.7, 147.6, 147.2, 144.4, 141.0, 139.0, 138.8, 137.5, 136.1, 134.6, 130.7, 130.0, 129.8, 129.2, 128.9, 128.7, 127.5, 127.3, 126.9, 126.4, 126.0, 125.2, 122.7, 122.2, 121.1, 119.9, 119.7, 118.4, 116.6, 110.7, 110.4, 108.5, 104.4, 103.3, 100.5, 98.1, 74.0, 72.1, 71.6, 71.4, 70.8, 67.4, 65.8, 63.7, 62.2, 61.6, 60.2, 56.0, 55.9, 55.0 and 32.9; and

(h) pK_a values in acetonitrile:water (3:7) as follows: 3.3, 7.1, 8.3, 9.1, 10.0 and 11.2 pK_a values above 11.2 not determined.

The AAD 216A pseudo-aglycone of the formula (I) wherein R_1 is hydrogen and R_2 is a glycolipid of unknown structure having an empirical formula $C_{16}H_{28}NO_6$ has the following characteristics:

(a) pale white-yellow solid which decomposes at 300—350°C.

(b) an empirical formula $C_{75}H_{72}N_8O_{25}Cl_4$;

(c) an approximate elemental composition of 49.76 percent carbon, 4.51 percent hydrogen, 5.99 percent nitrogen and 8.19 percent chlorine when the water content was 9.5 percent;

(d) an infrared absorption spectrum in potassium bromide which exhibits peaks at the following wave numbers in cm^{-1}: 3400, 2920, 1660, 1590, 1460, 1430, 1300, 1240, 1140, 1080, 1060 and 1010;

(e) a fast atom bombardment (FAB) mass spectrum with M + H at 1625 (major cluster);

(f) an ultraviolet spectrum in acetonitrile:water (1:1) which exhibits an absorption maximum at 281 nm under acidic conditions with an $E_{1\%}$ = 63.2 and at 302 nm under basic conditions with an $E_{1\%}$ = 94;

(g) a carbon magentic resonance spectrum at 90.56 MHz in $CD_3OD:D_2O$ (1:9) at a pH of 9.4 which exhibits the following chemical shifts in parts per million (ppm) relative to TMS as standard: 178.2, 178.0, 176.0, 175.6, 171.6, 170.9, 170.6, 170.5, 169.3, 164.6, 161.4, 159.3, 157.1, 156.5, 153.5, 152.5, 151.8, 151.1, 146.4, 144.9, 141.7, 138.6, 138.4, 136.9, 134.5, 134.4, 133.9, 130.8, 129.8, 129.7, 129.4, 128.6, 128.5, 128.3, 127.7, 127.3, 125.9, 125.7, 125.5, 122.5, 122.1, 120.1, 119.4, 118.0, 116.9, 109.6, 109.0, 108.7, 104.5, 104.4, 103.2, 98.9, 78.4, 74.3, 73.3, 72.1, 71.5, 66.2, 63.7, 61.9, 60.6, 56.9, 56.1, 55.8, 55.4, 37.2, 33.3, 32.0, 29.6, 29.4, 26.1, 22.9 and 14.4; and

(h) pK_a values in acetonitrile:water (3:7) as follows: 3.0, 4.3, 7.4, 8.5, 9.9 and 10.9 pK_a values above 10.9 not determined.

The AAD 216E pseudo-aglycone of the formula (I) wherein R_1 is hydrogen and R_2 is a glycolipid radical of unknown structure having an empirical formula $C_{17}H_{30}NO_6$ has the following characteristics:

(a) a white solid which decomposes at 250—300°C;

(b) a empirical formula $C_{76}H_{74}N_8O_{25}Cl_4$;

(c) an approximate elemental composition of 48.98 percent carbon, 4.56 percent hydrogen, 5.64 percent nitrogen and 8.29 percent chlorine when the water content was 6.9 percent;

(d) an infrared absorption spectrum in potassium bromide which exhibits peaks at the following wave numbers in cm^{-1}: 3400, 2920, 1660, 1590, 1500, 1480, 1430, 1300, 1240, 1150, 1080, 1060 and 1010;

(e) a fast atom bombardment (FAB) mass spectrum with M + H at 1639 (major cluster);

(f) an ultraviolet spectrum in acetonitrile:water (1:1) which exhibits an absorption maximum at 281 nm under acidic conditions with an $E_{1\%} = 61.8$ and at 303 nm under bascic conditions with an $E_{1\%} = 88$;

(g) a carbon magnetic resonance spectrum at 90.56 MHz in $CD_3OD:D_2O$ (1:9) at a pH of 9.4 which exhibits the following chemical shifts in parts per million (ppm) relative to TMS as standard: 178.3, 177.6, 175.9, 175.6, 171.5, 171.0, 170.7, 170.3, 169.4, 164.0, 159.3, 158.9, 156.4, 152.5, 151.7, 151.1, 146.2, 144.7, 141.8, 138.7, 138.6, 136.8, 134.4, 133.8, 130.9, 129.8, 129.5, 128.6, 128.4, 127.9, 127.3, 126.0, 125.8, 122.5, 119.9, 119.3, 118.2, 116.9, 109.3, 108.8, 104.3, 104.2, 103.0, 99.4, 78.7, 74.4, 73.5, 72.1, 71.6, 65.8, 63.8, 62.5, 60.6, 57.1, 56.1, 55.9, 55.4, 39.7, 37.3, 33.1, 30.3, 29.9, 29.7, 28.5, 28.0, 26.3 and 23.4.

The AAD 216C pseudo-aglycone of the formula (I) wherein R_1 is hydrogen and R_2 is a glycolipid radical of unknown structure having an empirical formula $C_{18}H_{32}NO_6$ has the following characteristics:

(a) a white solid which decomposes at 250—300°C;

(b) a empirical formula $C_{77}H_{76}N_8O_{25}Cl_4$;

(c) an approximate elemental compositions of 47.58 percent carbon, 4.51 percent hydrogen, 5.33 percent nitrogen and 8.08 percent chlorine when the water content was 7.8 percent;

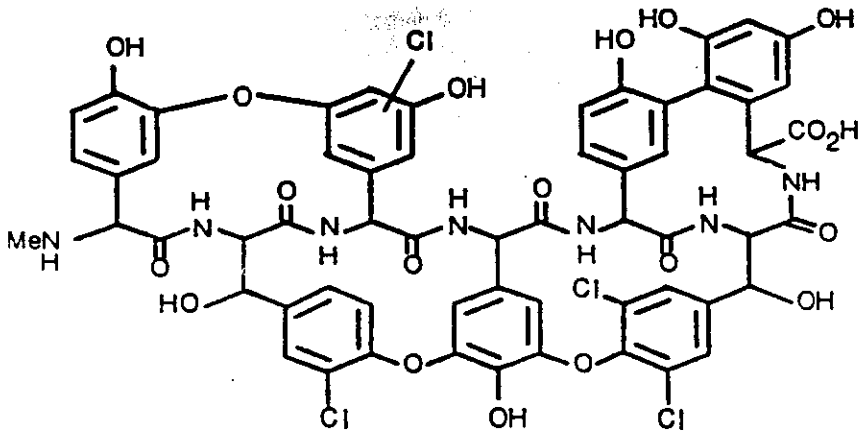
(d) an infrared absorption spectrum in potassium bromide which exhibits peaks at the following wave numbers in cm^{-1}: 3400, 2920, 1660, 1590, 1500, 1430, 1300, 1240, 1140, 1080, 1060 and 1010;

(e) a fast atom bombardment (FAB) mass spectrum with M + H at 1653 (major cluster);

(f) an ultraviolet spectrum in acetonitrile:water (1:1) which exhibits an absorption maximum at 281 nm under acidic conditions with an $E_{1\%} = 60.0$ and at 303 nm under bascic conditions with an $E_{1\%} = 83$;

(g) a carbon magnetic resonance spectrum at 90.56 MHz in $CD_3OD:D_2O$ (1:9) at a pH of 9.4 which exhibits the following chemical shifts in parts per million (ppm) relative to TMS as standard: 178.1, 177.4, 175.5, 175.4, 171.4, 171.0, 170.7, 170.3, 169.3, 163.6, 159.1, 158.6, 156.5, 156.2, 152.7, 151.9, 151.8, 151.0, 146.2, 144.6, 142.0, 138.8, 138.6, 136.9, 134.8, 134.7, 134.0, 130.6, 129.9, 129.8, 129.4, 128.8, 128.3, 127.8, 127.5, 127.2, 126.4, 126.2, 125.8, 122.5, 122.0, 119.6, 119.1, 118.4, 116.9, 109.5, 109.2, 108.7, 104.2, 103.6, 99.8, 78.6, 74.6, 73.5, 72.1, 71.7, 66.0, 63.7, 62.1, 60.6, 56.9, 56.1, 55.9, 55.4, 39.6, 37.3, 33.2, 30.4, 30.0, 29.8, 28.5, 27.9, 26.3 and 23.1.

The AAD 216 aglycone, represented by the structural formula (II)



(II)

has the following characteristics:

(a) a pale white-yellow solid which decomposes at 300 350°C;

(b) an empirical formula $C_{59}H_{45}N_7O_{19}Cl_4$;

(c) an approximate elemental composition of 47.92 percent carbon, 3.78 percent hydrogen, 6.58 percent nitrogen and 9.50 percent chlorine when the water content was 10.70 percent;

(d) an infrared absorption spectrum in potassium bromide which exhibits peaks at the following wave numbers in cm^{-1}: 3400, 1660, 1610, 1590, 1510, 1460, 1430, 1390, 1300, 1240, 1150, 1080, 1060 and 1010;

(e) a fast atom bombardment (FAB) mass spectrum with M + H at 1296 (major cluster);

(f) an ultraviolet spectrum in acetonitrile:water (1:1) which exhibits an absorption maximum at 281 nm under acidic conditions with an $E_{1\%}$ = 83 and at 300 nm under bascic conditions with an $E_{1\%}$ = 140;

(g) a carbon magnetic resonance spectrum at 90.56 MHz in $(CD_3)_2SO$ at a pH of 3.3 which exhibits the following chemical shifts in parts per million (ppm) using TMS as the internal standard: 172.6, 172.1, 170.0, 169.2, 168.4, 167.2, 167.0, 157.2, 156.4, 155.5, 155.0, 154.6, 151.4, 147.5, 145.8, 144.7, 142.8, 141.7, 139.0, 138.7, 136.2, 135.6, 134.5, 128.5, 128.2, 128.0, 127.9, 127.8, 127.4, 127.3, 126.3, 126.0, 125.3, 125.0, 121.1, 118.1, 117.7, 117.5, 116.6, 113.7, 108.7, 106.3, 105.9, 105.4, 103.7, 102.5, 71.3, 70.1, 65.3, 61.4, 60.1, 56.8, 54.8, 53.9, 53.6 and 33.4; and

(h) pK_a values in acentonitrile:water (3:7) as follows: 3.3, 7.1, 8.4, 9.2, 10.1 and 11.4 pK_a values above 11.4 not determined.

The compounds of the instant invention are conveniently prepared from the AAD 216 antibiotics along the following lines:

The AAD 216 pseudo-aglycone is prepared by hydrolyzing the AAD 216 antibiotics, exemplified by AAD 216A, in aqueous organic solvent and very dilute mineral acid at reflux until a substantial amount of the AAD 216 pseudo-aglycone is formed and subsequently isolating it from the reaction mixture. Illustrative of this hydrolysis process is the treatment of AAD 216A in 10 percent aqueous acetonitrile with 0.001 N hydrochloric at reflux for 48 hours and the isolation of the AAD 216 pseudo-aglycone by chromatographic means.

The AAD 216 aglycone, the AAD 216A pseudo-aglycone, AAD 216B pseudo-aglycone and AAD 216C pseudo-aglycone are prepared by the hydrolysis of the appropriate AAD 216A, AAD 216B and AAD 216C in a polar organic solvent and dilute mineral acid at elevated temperature until a substantial amount of the hydrolysis products are formed and subsequently isolating the individual desired products. Illustrative of this hydrolysis process is the treatment of AAD 216A in dimethylsulfoxide with 5 percent hydrochloric acid at 100°C for 15 minutes. The isolation of the individual AAD 216 aglycone and the AAD 216A pseudo-aglycone may be accomplished by chromatographic means.

Alternatively, the AAD 216 aglycone and the pseudo-aglycones may be prepared by the mild acid hydrolysis of the AAD 216 complex or the individual factors followed by a chromatographic isolation of the desired compounds.

Biological Activity Data

The *in vitro* minimum inhibitory concentrations (MIC) of the AAD 216 aglycone, AAD 216 pseudo-aglycone, AAD 216A pseudo-aglycone, AAD 216B pseudo-aglycone, AAD 216C pseudo-aglycone and vancomycin were determined for a number of microorganisms using the standard microtiter assay procedures. The AAD 216 aglycone, the AAD 216 pseudo-aglycone, the AAD 216A pseudo-aglycone, the AAD 216B pseudo-aglycone and the AAD 216C pseudo-aglycone were neutralized with sodium bicarbonate prior to testing. The results are shown in the following Tables A—F.

Antimicrobial Spectrum

TABLE A

Test Organism	MIC in µg/ml			
	AAD 216 Aglycone	AAD 216 Pseudo-Aglycone	AAD 216A Pseudo-Aglycone	Vancomycin
Staph. aureus HH127	0.4	1.6	0.8	1.6
Staph. aureus SK&F 910	0.4	1.6	0.4	1.6
Strep. faecilis HH34358	0.8	1.6	0.4	3.1
Proteus mirabilis SK&F 444	25	100	100	110
E. coli 12140 (SK&F 809)	100	>100	>100	100
k. pneumoniae 4200 (SK&F 798)	>100	>100	>100	>100
Pseudomonas aeruginosa HH63	>100	>100	>100	>100
Serratia marcesens ATCC 13880	>100	>100	>100	>100
Proteus morgani SK&F 179	>100	>100	>100	>100
Providencia SK&F 276	>100	>100	>100	>100
Enterobacter cloacae HH31254	>100	>100	>100	>100
Salmonella galllinarum SK&F BC595	25	25	~100	25
Staph. epidermidis SK&F 2479	0.8	~3.1	0.8	1.6
Listeria monocytogenes SK&F 2255	0.8	1.6	0.4	1.6
Staph. epidermidis SK&F 651	3.1	12.5	3.1	1.6

TABLE B

(Methicillin Sensitive)

Test Organism	MIC in µg/ml			
	AAD 216 Aglycone	AAD 216 Pseudo-Aglycone	AAD 216A Pseudo-Aglycone	Vancomycin
Staph. aureus HH127	0.4	1.6	0.4	1.6
Staph. aureus SK&F 674	0.8	3.1	0.8	1.6
Staph. aureus SK&F 910	0.8	3.1	0.4	1.6
Staph. aureus SK&F 1761	0.8	3.1	0.4	1.6
Staph. aureus SK&F 2666	0.8	3.1	0.4	1.6
Staph. aureus SK&F 2677	0.8	3.1	0.4	1.6
Staph. aureus SK&F 2678	0.8	3.1	0.4	1.6
Staph. aureus SK&F 2680	0.8	3.1	0.8	1.6
Staph. aureus SK&F 2682	0.8	3.1	0.4	1.6
Staph. aureus SK&F 2736	0.8	3.1	0.8	1.6
Staph. aureus SK&F 2743	0.8	3.1	0.8	1.6
Staph. aureus SK&F 2776	3.1	3.1	1.6	1.6
Staph. aureus SK&F 2777	0.4	1.6	0.4	0.8
Staph. aureus SK&F 2613	0.4	1.6	0.4	1.6
Staph. aureus SK&F 2615	0.8	3.1	0.8	3.1

TABLE C
(Methicillin Resistant)

Test Organism	MIC in µg/ml			
	AAD 216 Aglycone	AAD 216 Pseudo-Aglycone	AAD 216A Pseudo-Aglycone	Vancomycin
Staph. aureus SK&F 675	0.8	3.1	0.8	1.6
Staph. aureus SK&F 2612	0.8	3.1	~0.8	1.6
Staph. aureus SK&F 2614	0.4	0.8	0.2	1.6
Staph. aureus SK&F 2616	0.4	1.6	0.2	0.8
Staph. aureus SK&F 2620	0.8	3.1	0.8	3.1
Staph. aureus SK&F 2621	0.4	1.6	0.4	1.6
Staph. aureus SK&F 2594	0.4	3.1	0.4	1.6
Staph. aureus SK&F 2589	0.4	3.1	0.4	1.6
Staph. aureus SK&F 2590	0.4	3.1	0.4	1.6
Staph. aureus SK&F 2593	0.8	3.1	0.8	1.6
Staph. aureus SK&F 2591	0.8	3.1	0.8	1.6
Staph. aureus SK&F 2592	0.8	3.1	1.6	3.1
Staph. aureus SK&F 2595	0.8	3.1	1.6	1.6
Staph. aureus SK&F 2596	0.4	3.1	1.6	3.1
Staph. aureus SK&F 2597	0.8	3.1	1.6	3.1

TABLE D
(Anaerobes)

Test Organism	MIC in µg/ml			
	AAD 216 Aglycone	AAD 216 Psuedo-Aglycone	AAD 216A Pseudo-Aglycone	Vancomycin
Bacteroides fragilis ATCC 25285	32	>32	16	32
B. fragilis H145	32	>32	8	32
B. fragilis SK&F 3060	32	>32	16	32
B. loeochis SK&F 3087	16	32	8	32
B. thetaiotamicron SK&F 3089	32	>32	16	32
Fusobacterium nucleatum ATCC 25586	32	>32	16	32
Clostridium perfringens MCP-1	≤0.016	≤0.016	≤0.016	0.5
C. perfringens MCP-2	≤0.016	0.031	≤0.016	0.5
C. perfringens ATCC 19408	0.5	0.05	0.125	1.0
Clostridium difficile SK&F 3062	2	2	0.125	2
C. difficile SK&F 3065	2	2	0.25	2
C. difficile SK&F 3091	≤0.016	≤0.016	0.125	2
C. difficile SK&F 3092	2	2	0.125	2
C. difficile SK&F 3096	1.0	2	0.25	2
C. difficile SK&F 3098	≤0.016	≤0.016	≤0.016	2

TABLE E

Test Organism	MIC in µg/ml			
	AAD 216A Pseudo-Aglycone	AAD 216B Psuedo-Aglycone	AAD 216C Pseudo-Aglycone	Vancomycin
Staph. aureus HH127	0.4	0.4	0.2	0.2
Staph. aureus SK&F 910	0.4	0.2	0.8	1.6
Staph. aureus SK&F 209P	0.1	0.2	0.1	1.6
Staph. aureus SK&F 209P-mutant	100	50	50	100
Staph. aureus SK&F 674-P6-mutant	50	50	25	100
Staph. aureus SK&F 675	1.6	1.6	3.1	3.1
Staph. epidermidis SK&F 2479	3.1	6.3	6.3	3.1
Staph. epidermidis SK&F 2683	6.3	3.1	6.3	3.1
Staph. epidermidis SK&F 651	12.5	12.5	12.5	3.1
Staph. epidermidis SK&F 2265	12.5	6.3	12.5	3.1
Staph. faecalis SK&F 34358	0.2	0.1	0.1	3.1
Staph. faecalis SK&F 657	0.4	0.1	0.1	3.1
Listeria monocytogenes SK&F 2255	0.1	0.1	0.1	0.8
E. coli. SK&F 12140	>100	>100	>100	>100
Salmonella gallinarum BC-595	>100	>100	>100	>100

TABLE F

Test Organism	MIC in µg/ml AAD 216A Pseudo-Aglycone	AAD 216B Psuedo-Aglycone	AAD 216C Pseudo-Aglycone	Vancomycin
Bacteroides Fragilis ATCC	>32	>32	32	>32
B. thetaiotomicron H-145	>32	>32	>32	>32
Fusobacterium nucleatum ATCC 25586	>32	16	16	32
C. perfringens SK&F 2769	0.063	0.031	0.125	0.5
C. perfringens MCP-2	0.5	0.5	0.5	2.0
C. difficile SK&F 3062	0.125	0.125	0.125	0.5
C. difficile SK&F 3065	0.25	0.25	0.25	1.0
C. difficile SK&F 3092	0.25	0.25	0.5	0.5
C. difficile SK&F 3141	0.5	0.25	0.5	1.0

The *in vivo* activity of the AAD 216 aglycone, AAD 216 pseudo-aglycone, AAD 216A pseudo-aglycone and vancomycin, measured as ED_{50}, was demonstrated against intraperitoneal infections with 46.8 LD_{50}'s of *Staph. aureus* HH 127 in mice by treatments with the antibiotics s.c., 1 and 5 hours post infection. The ED_{50}'s were as follows: AAD 216 aglycone, 7.6 mg/kg; AAD 216 pseudo-aglycone, 7.6 mg/kg; AAD 216A pseudo-aglycone, 5.0 mg/kg; vancomycin, 1.56 mg/kg. Similarly, the ED_{50}'s of AAD 216A pseudo-aglycone, AAD 216B pseudo-aglycone, AAD 216C pseudo-aglycone and vancomycin, determined by utilizing a similar protocol, were 12.5 mg/kg, 7.6 mg/kg, 10.8 mg/kg and 1.92 mg/kg, respectively.

The antibiotic compounds of the present invention including AAD 216 aglycone, AAD 216 pseudo-aglycone and AAD 216A pseudo-aglycone, AAD 216B pseudo-aglycone, AAD 216C pseudo-aglycone and mixtures thereof, exhibit antibacterial activity. The invention includes within its scope pharmaceutical compositions containing at least one of the above-mentioned antibiotic compounds and a pharmaceutically acceptable carrier. The compositions may also contain other active antibacterial agents. The compositions may be made up in any pharmaceutical form appropriate for the route of administration in question. Such compositions are exemplified by solid compositions for oral administration, such as tablets, capsules, pills, powders and granules; liquid compositions for oral administration such as solutions, suspensions, syrups and elixers; and preparations for parenteral administration such as sterile solutions, suspensions or emulsions.

For use as an antibacterial agent, the compositions are administered so that the concentration of the active ingredient is greater than the minimum inhibitory concentration for the particular organism treated.

The activity of the AAD 216 aglycone, AAD 216 pseudo-aglycone and AAD 216A pseudo-aglycone was demonstrated *in vitro* against a total of 58 bovine mastitis isolates using the conventional agar dilution method to determine minimum inhibitory concentrations (MICs). The MICs for AAD 216 aglycone, AAD 216 pseudo-aglycone and AAD 216 pseudo-aglycone ranged from 0.5 to >128 µg/ml, 0.25 to >128 µg/ml and 0.03 to >128 µg/ml, respectively. In comparison, vancomycin has MICs for the same microorganisms ranging from 0.25 to >128 µg/ml.

Growth Promotant Activity

The growth promotant activities of the AAD 216 aglycone, AAD 216 pseudo-aglycone, and AAD 216A pseudo-aglycone were determined in a swine *in vitro* model to predict utility in monogastric animals, such as swine and poultry; and a rumen *in vitro* model to predict utility in beef, dairy and sheep production.

Swine *in vitro* model

A Yorkshire barrow is surgically prepared either with an ileal cannula, which is placed 15 cm from the ileo-ceocolic junction, or a cecal cannula, which placed midway between the apex and origin of the cecum. The animal is fed 4 times daily to restrict intake to 4.5% of body weight in a 30 kg animal or 2.5% of body weight in a 100 kg animal. The swine grower ration is:

	(% w/w)	(lbs/ton)
Medium ground shelled corn	70.60	1412
Soybean meal, 44%	22.00	440
Dehydrated alfalfa mea, 17%	4.50	90
Calcium propionate	0.15	3
Vitamin/mineral premix	2.75	55

Sampling of the material, via the cannula, begins 150—180 minutes following the first morning feeding and continues any time from 30—120 minutes thereafter, depending on the quantity of material needed. The sample is maintained in crushed ice, no cooler than 5°C, and is gassed continuously with carbon dioxide. The collected material is filtered. The filtrate is the inoculum used for incubations of the test and control samples. The gassed inoculum, 2.25 ml, is placed in each of 10 gassed test tubes, each containing 0.75 ml of a nutrient solution and 0.5 mg of each test compound. Four blank control tubes, along with the test compound tubes, are incubated 5 hours at 37°C with agitation. Four more killed tubes are included which are not incubated.

The tubes are each treated with 0.60 ml of a 25% solution of metaphosphoric acid, then, stored at −4°C until analysis. Samples are thawed and centrifuged for 25 minutes at 20,000 r.p.m. The supernatent liquid is decanted, sampled for gas chromatography and automatic analysis. The results are fed into a computer for finishing to give figures in which the blank control value is 100%; see the following tables. Virginiamycin and vancomycin or avoparcin are used as positive controls.

I. Compound (ppm)	VFA* (% Control)	LYS* (% Control)	GLU* (% Control)	LAC* (% Control)
Virginiamycin				
(166.67)	93	163	197	81
(16.67)	130	127	191	76
(1.67)	248	82	182	70
Vancomycin				
(166.67)	250	48	190	64
(16.67)	280	42	189	59
(1.67)	92	83	100	99
AAD 216 Aglycone				
(166.67)	255	65	180	62
(16.67)	307	39	182	58
(1.67)	86	91	94	101
AAD 216 Pseudo-aglycone				
(166.67)	266	64	183	62
(16.67)	238	76	171	69
(1.67)	96	110	94	101
AAD 216A Pseudo-aglycone				
(166.67)	302	52	187	58
(16.67)	361	59	184	58
(1.67)	106	106	101	98

II.

Compound (ppm)	VFA* (% Control)	LYS* (% Control)	GLU* (% Control)	LAC* (% Control)
Virginiamycin				
(1.67)	240	96	837	21
Avoparcin				
(1.67)	85	101	115	102
AAD 216B Pseudo-aglycone				
(16.67)	313	96	894	16
(1.67)	118	102	169	95
AAD 216C Pseudo-aglycone				
(16.67)	252	91	895	16
(1.67)	131	94	225	85

*VFA refers to the total of volatile fatty acids, namely acetate, propionate, isobutyrate, butyrate, isovalerate and valerate. LYS is lysine, GLU is glucose and LAC is L-lactic acid.

Rumen *in vitro* model

The protocol for the rumen *in vitro* model is analogus to the protocol for the swine *in vitro* model with the following modifications:

(1) A 400 kg steer is surgically prepared with a rumen cannula.

(2) The animal is fed one time a day with the following ration:

Finished Feed	% w/w
Cottonseed hulls	44.0
Cracked corn	22.0
Alfalfa Hay 1''	20.0
Pellet Supplement*	10.0
Liquid Molasses	4.0
	100.0

* Pellet Supplement	% w/w
Soybean Oil Meal (50% protein)	50.0
Medium Ground Corn	32.5
D/Calcium Phosphate	6.50
Plain Salt	2.50
Ground limestone (Thomasville)	3.50
Urea	2.50
Vitamin A & D_2 Premix **	2.50
	100.00

**Vitamin A & D_2 Premix	% w/w
Vitamin A (30,000 IU/gm)	5.87
Vitamin D_2 (16,000,000 IU/lb)	0.50
Fine ground corn	93.63
	100.00

(3) Manipulation of VFA production is described as the production ratio of propionate as a percentage of total VFA produced.

(4) Sampling of the material, via the cannula, is at 120 minutes post feeding.

III.

Compound (ppm)	VFA* (% Control)	LYS* (% Control)	GLU* (% Control)	Propionate* (% Control)
Vancoymycin				
(50.0)	107	97	189	127
(5.0)	108	85	165	130
(0.5)	97	83	17	105
Avoparcin				
(50.0)	113	97	141	132
(5.0)	105	85	166	121
(0.5)	103	96	116	106
Monensin Sodium				
(50.0)	109	147	0	156
(5.0)	104	141	126	149
(0.5)	94	109	11	119
AAD 216 Aglycone				
(50.0)	93	99	14	135
(5.0)	110	101	22	131
(0.5)	100	98	0	102
AAD 216 Pseudo-aglycone				
(50.0)	104	101	104	127
(5.0)	95	96	0	15
(0.5)	88	118	47	101
AAD 216A Pseudo-aglycone				
(50.0)	113	115	38	149
(5.0)	110	97	30	139
(0.5)	98	102	534	106

IV.

Compound (ppm)	VFA* (% Control)	LYS* (% Control)	Propionate* (% Control)
Avoparcin			
(5.0)	109	157	122
Monensin Sodium			
(5.0)	106	595	161
AAD 216B Pseudo-aglycone			
(5.0)	114	163	125
(0.5)	100	55	99
AAD 216C Pseudo-aglycone			
(5.0)	104	99	133
(0.5)	104	65	100

*VFA refers to the total of volatiles fatty acids, namely acetate, propionate, isobutyrate, butyrate, isovalerate and valerate. LYS is lysine, and GLU is glucose.

The feed compositions of this invention comprise the normal feed rations of the meat and milk producing animals supplemented by a quantity of an active ingredient selected from the group consisting of AAD 216 aglycone, AAD 216 pseudo-aglycone, AAD 216A pseudo-aglycone, AAD 216B pseudo-aglycone, AAD 216C pseudo-aglycone or a mixture thereof which is effective for improving the growth rate and feed efficiency of the animals but which is not toxic or noxious to a degree that the animals will reduce ingestion of the ration. The quantity of the active ingredient will vary, as is known to the art, with factors such as the cost of the ingredient, the species and the size of animal, the relative activity of the compound formula I or the type of feed ration used as the basal feed.

Representative feed rations for swine and poultry are as follows:

A swine ration for growing hogs of 40—100 pounds body weight is prepared using the following formula:

Corn, ground	78.15%
Soybean oil meal, 44%	17.0%
Meat scraps, 50%	3.0%
Oyster shell flavor	0.4%
Bone meal	0.5%
Zinc oxide	0.01%
Vitamin A, B, B_{12} & D supplement	optional

A chicken ration for broilers is prepared using the following formula:

Yellow corn meal	67.35%
Soybean oil meal	24.00%
Menhaden fish meal	6.00%
Steamed bone meal	1.00%
Ground limestone	1.00%
Iodized salt	0.34%
25% choline chloride	0.13%
Vitamin B_{12}	0.10%
Manganese sulfate	0.02%
Vitamin mix	0.06%

Swine feed from weanling to fattening or finishing rations may be supplemented. Swine eat from about 2 lb of ration per day (for a 25 lb pig) to 9 lb per day (for a 150 lb pig). Most rations are comprised of a corn base supplemented with legume silage, wheat bran, oats, barley, molasses or a protein supplement.

Poultry feeds comprise starter rations, broiler rations and laying rations. The rations are usually based on ground corn, corn meal or soybean meal. The broiler rations, often, contain high energy supplements such as added fats, proteins and vitamins. Turkey rations are similar, but comprise only a starting ration and a growing ration. Chickens or pheasants eat from .03—0.3 lbs of feed per day, turkeys twice that much. Estimated intake of feed is dependent on the weight and age of the meat producing animal.

The active ingredients selected from the group consisting of AAD 216 aglycone, AAD 216 pseudo-aglycone, AAD 216A pseudo-aglycone, AAD 216B pseudo-aglycone, AAD 216C pseudo-aglycone or a mixture thereof are mixed uniformly with such feed rations to give supplemented rations which are, then fed as to custom, which is, most often, ad libitum. Conveniently, to do this, a premix of the supplemental growth promotant of this invention, optionally combined with or without other supplements known to this art such as an anthelmintic, a nitrogen source or an antibiotic, for example, virginiamycin or oxytetracycline is prepared by the manufacturer for sale to the formulators or feed lot operators. The concentration of the active ingredients selected from the group consisting of AAD 216 aglycone, AAD 216 pseudo-aglycone, AAD 216A pseudo-aglycone, AAD 216B pseudo-aglycone, AAD 216C pseudo-aglycone or a mixture thereof in the premix is usually from 5—75% by weight or a concentration 100—2000 times greater than that in the complete feed ration. The premix form may be liquid or solid. Premix vehicles are corn oil, cottonseed oil, molasses or distillers solubles to form a liquid premix preparation. Sucrose, lactose, corn meal, ground corn, flour, calcium carbonate or soybean meal are often used as bases for solid premix preparations. The premix composition is, then, mixed uniformly with whole ration which is fed to the target animal. Such premix compositions are included in the term "feed compositions" as used herein.

The concentration of the active ingredients selected from the group consisting of AAD 216 aglycone, AAD 216 pseudo-aglycone, AAD 216A pseudo-aglycone, AAD 216B pseudo-aglycone, AAD 216C pseudo-aglycone or a mixture thereof in the complete ration is a nontoxic but active quantity chosen, for example, from a range of about 1—1000 parts of active ingredient by weight per million parts of whole feed (ppm) or about 2—115 grams per ton. Advantageously, a nontoxic quantity of active ingredient is chosen from the range of 10—50 ppm.

The method of this invention comprises feeding to monogastric or ruminant, meat or milk producing animals, especially beef and dairy cattle, sheep, swine and poultry, an effective promoting but nontoxic quantity of an active ingredient selected from the group consisting of AAD 216 aglycone, AAD 216 pseudo-aglycone, AAD 216A pseudo-aglycone, AAD 216B pseudo-aglycone, AAD 216C pseudo-aglycone or a mixture thereof. Other monogastric animals whose digestive tract also features fermentation in a cecum or cecum-like chamber are rabbits and horses.

The supplemented feed rations, described above, are presented to the animal by methods known to the art. Ad libitum feeding in the pasture, pen or growing shed is most convenient to increase the growth and milking rate of the animal and to increase the feed efficiency of the operation.

The following examples are illustrative of the production, isolation and purification of the antibiotics of the present invention and are not therefore to be considered in limiting the present invention as described in the claims appended hereto.

Example 1

Preparation of AAD 216 pseudo-aglycone

AAD 216A (1.2 g) was partially dissolved in 10 percent aqueous acetonitrile and 0.0001 N hydrochloric

acid (total volume 1500 ml) and heated to reflux for 48 hours. The reaction mixture was lyophilized and then chromatographed on reverse phase HPLC with a column of Whatman Partisil 40® (ODS-3) (25 × 500 mm) at a flow rate of 15 ml/minute. The column was eluted with 15 percent acentonitrile — 0.1 M pH 3.2 phosphate buffer (2000 ml) and 18 percent acetonitrile — buffer solution (1000 ml). The appropriate fractions were combined, lyophilized and desalted as described below to yield the desired AAD 216 pseudo-aglycone.

The desalting procedure involved a pooling of the appropriate fractions from the HPLC and removal of the acetonitrile at reduced pressure. The resulting aqueous samples were loaded onto an XAD-7 resin column and eluted with deionized water until the conductivity of the outflow was less than 1.5 µMHO. The column was then eluted with aqueous acetonitrile (50%) and the eluant lyophilized to afford the desired prodcuts.

Example 2

Preparation of AAD 216 aglycone and AAD 216A pseudo-aglycone

AAD 216 (0.74 g) was dissolved in 5 percent concentrated hydrochloric acid and dimethylsulfoxide (40 ml) and heated for 15 minutes at 100°C. The reaction mixture was diluted with 14 percent acetonitrile 0.1 M pH 3.2 phosphate buffer and chromatographed with the equipment described in Example 1. The column was eluted with 14 percent acetonitrile-buffer solution (1000 ml) followed by 18 percent (500 ml), 22 percent (500 ml), 26 percent (500 ml) and 30 percent (1000 ml) acetonitrile-buffer solution. The appropriate fractions containing AAD 216A pseudo-aglycone were combined and the appropriate fractions containing AAD 216 aglycone were combined. Both of the combined fractions were separately lyophilized and desalted using the procedure in Example 1 to afford the desired products.

Example 3

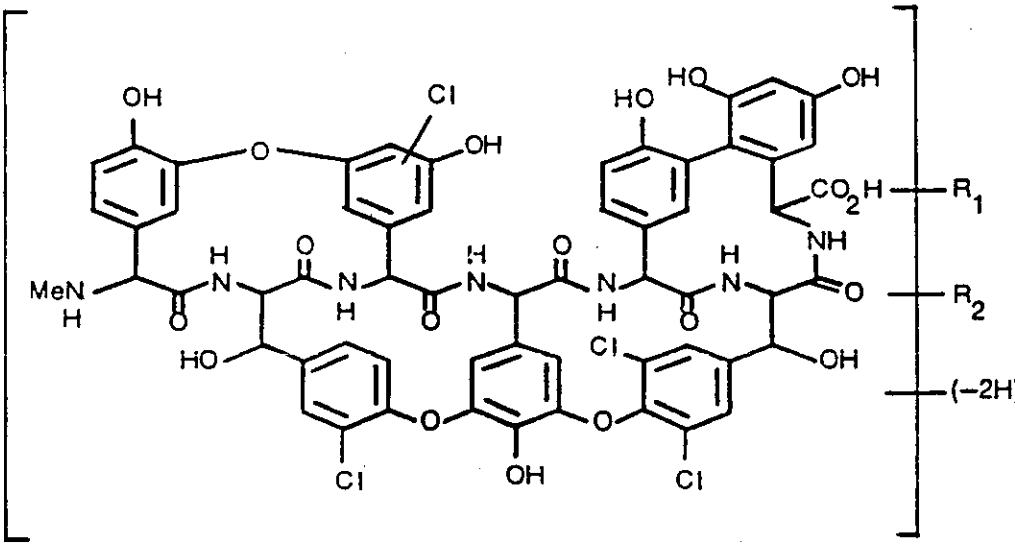
Preparation of AAD 216B Pseudo-Aglycone

AAD 216B (1.64 g) was dissolved in dimethylsulfoxide (40 ml) and concentrated hydrochloric acid (2 ml) was added. The reaction mixture was heated at 100°C for 15 minutes and then diluted with 31 percent acetonitrile 0.1 M pH 6.0 phosphate buffer (450 ml) which was loaded onto an affinity chromatography column (700 ml — Affigel 10 D-ala-D-ala). The column was washed with 0.1 M pH 6.0 phosphate buffer (100 ml), water (2000 ml) and 1 percent aqueous acetonitrile (1000 ml). The reaction products were eluted off the affinity chromatography column with 50 percent acetonitrile in 0.15 N ammonia (2000 ml). The eluant was lyophilized, dissolved in 10 percent acetonitrile in 0.1 M pH 6.0 phosphate buffer and chromatographed on the equipment described in Example 1. The column was eluted with 10 percent acetonitrile in 0.1 M pH 6.0 phosphate buffer (500 ml), followed by 15 percent (750 ml), 18 percent (750 ml), 22 percent (500 ml), 26 percent (50 ml), 30 percent (500 ml) and 35 percent (1000 ml) acetonitrile buffer solution. The appropriate factions containing AAD 216B pseudo-aglycone were combined and the fractions containing AAD 216 aglycone were combined. Both combined fractions were separately lyophilized and desalted using the procedure in Example 1 to afford the desired products.

Utilizing the procedure of Example 3, AAD 216C (2.0 g) was hydrolyzed to yield AAD 216C pseudo-aglycone and AAD 216 aglycone. AAD 216A pseudo-aglycone was also prepared via the procedure of Example 3.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

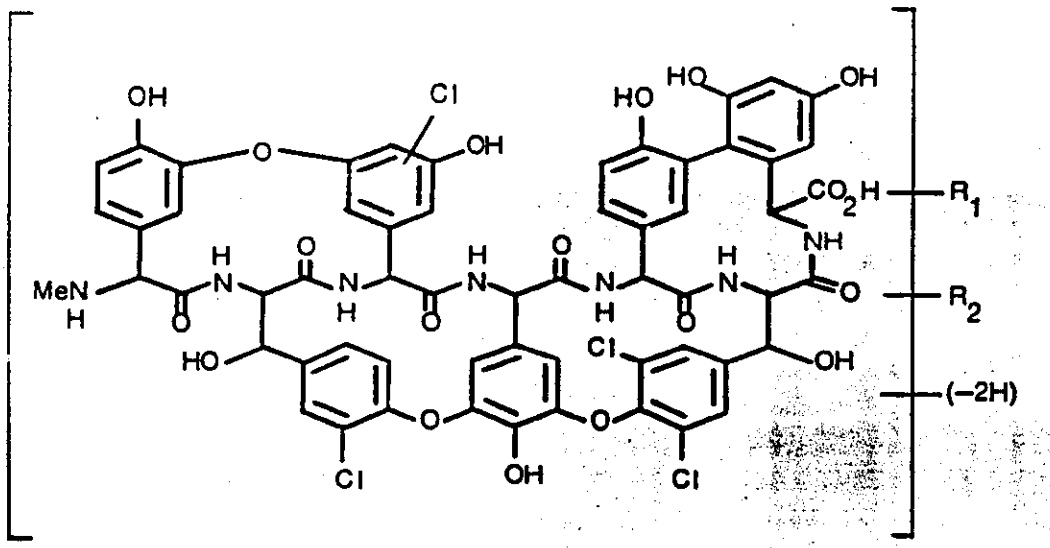
1. An antibiotic compound represented by the structural formula (I)



(I)

wherein R_1 is hydrogen or mannosyl and R_2 is hydrogen or a glycolipid radical of unknown structure with the proviso that at least one of R_1 and R_2 is hydrogen, prepared by the removal by acid hydrolysis of a glycolipid radical and/or a mannosyl radical from an antibiotic selected from the group consisting of AAD 216 complex, AAD 216A, AAD 216B and AAD 216C.

2. An antibiotic compound represented by the structural formula (I)



(I)

wherein R_1 is mannosyl and R_2 is hydrogen having the following characteristics:

(a) pale white-yellow solid which decomposes at 300—350°C;

(b) an empirical formula $C_{55}H_{55}N_7O_{24}Cl_4$;

(c) an approximate elemental composition of 47.54 percent carbon, 4.00 percent hydrogen, 5.89 percent nitrogen and 8.63 percent chlorine when the water content was 12 percent;

(d) an infrared absorption spectrum in potassium bromide which exhibits peaks at the following wave numbers in cm^{-1}: 3400, 1660, 1610, 1590, 1510, 1460, 1430, 1390, 1300, 1230, 1180, 1150, 1120, 1060, 1010, 970 and 801;

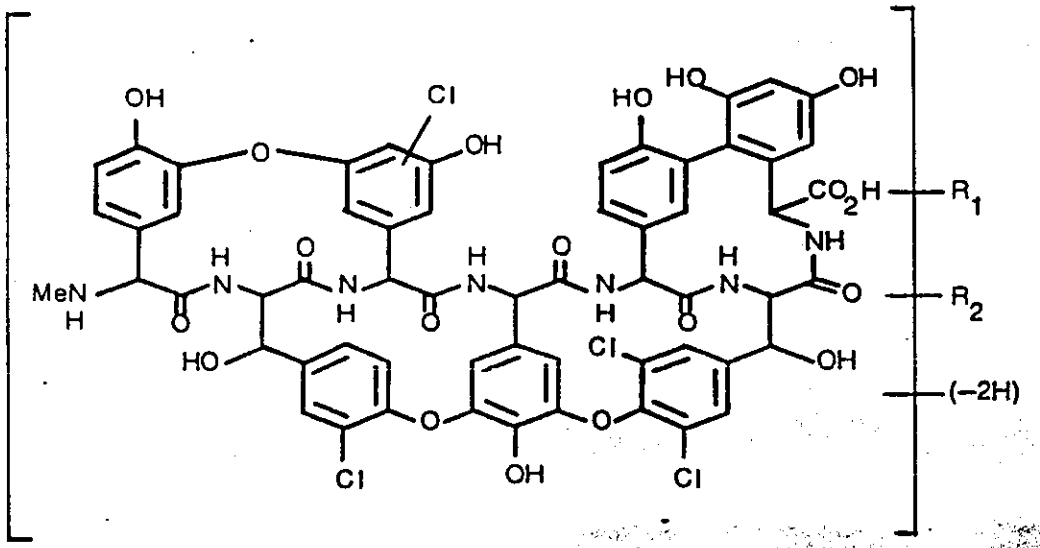
(e) a fast atom bombardment (FAB) mass spectrum with M + H at 1458 (major cluster);

(f) an ultraviolet spectrum in acetonitrile:water (1:1) which exhibits an absorption maximum at 281 nm under acid conditions with an $E_{1\%}$ = 79.7 and at 300 nm under basic conditions with an $E_{1\%}$ = 136;

(g) a carbon magnetic resonance spectrum at 90.56 MHz in CD_3OD:D_2O (1:9) at a pH of 8.7 which exhibits the following chemical shifts in parts per million (ppm) relative to TMS as standard: 177.9, 174.6, 171.7, 170.9, 170.0, 169.2, 162.3, 158.8, 157.9, 155.2, 155.1, 153.9, 151.9, 149.7, 147.6, 147.2, 144.4, 141.0, 139.0, 138.8, 137.5, 136.1, 134.6, 130.7, 130.1, 129.8, 129.2, 128.9, 128.7, 127.5, 127.3, 126.9, 126.4, 126.0, 125.2, 122.7, 122.2, 121.1, 119.9, 119.7, 118.4, 116.6, 110.7, 110.4, 108.5, 104.4, 103.3, 100.5, 98.1, 74.0, 72.1, 71.6, 71.4, 70.8, 67.4, 65.8, 63.7, 62.2, 61.6, 60.2, 56.0, 55.9, 55.0 and 32.9; and

(h) pK_a values in acetonitrile:water (3:7) as follows: 3.3, 7.1, 8.3, 9.1, 10.0 and 11.2 pK_a values above 11.2 not determined.

3. An antibiotic compound represented by the structural formula (I):



(I)

wherein R_1 is hydrogen and R_2 is a glycolipid of unknown structure having an empirical formula $C_{16}H_{28}NO_6$ and having the following characteristics:

(a) pale white-yellow solid which decomposes at 300–350°C;

(b) an empirical formula $C_{75}H_{72}N_8O_{25}Cl_4$;

(c) an approximate elemental composition of 49.76 percent carbon, 4.51 percent hydrogen, 5.99 percent nitrogen and 8.19 percent chlorine when the water content was 9.5 percent;

(d) an infrared absorption spectrum in potassium bromide which exhibits peaks at the following wave numbers in cm^{-1}: 3400, 2920, 1660, 1590, 1500, 1460, 1430, 1300, 1240, 1140, 1080, 1060 and 1010;

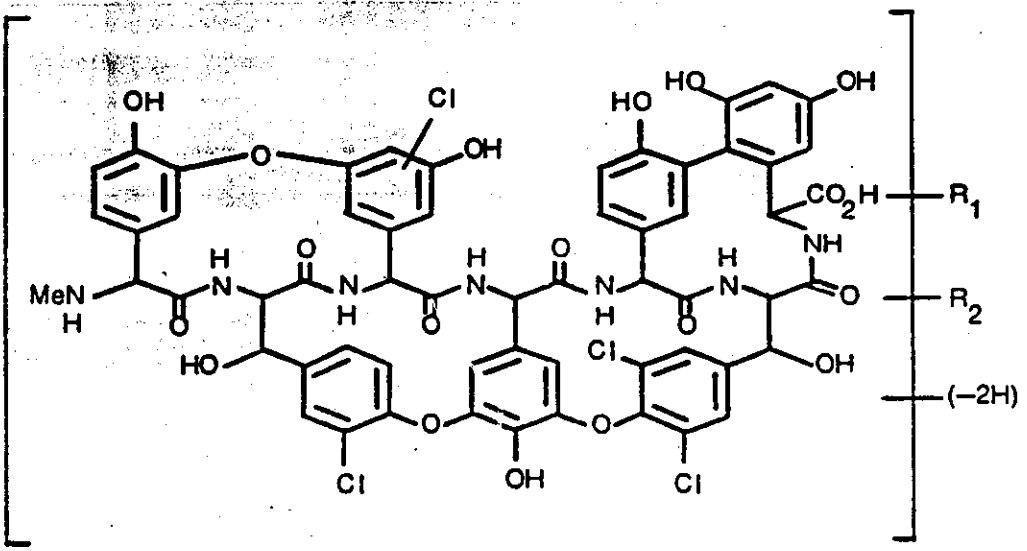
(e) a fast atom bombardment (FAB) mass spectrum with M + H at 1625 (major cluster);

(f) an ultraviolet spectrum in acetonitrile:water (1:1) which exhibits an absorption maximum at 281 nm under acidic conditions with an $E_{1\%}$ = 63.2 and at 302 nm under basic conditions with an $E_{1\%}$ = 94;

(g) a carbon magnetic resonance spectrum at 90.56 MHz in $CD_3OD:D_2O$ (1:9) at a pH of 9.4 which exhibits the following chemical shifts in parts per million (ppm) relative to TMS as standard: 178.2, 178.0, 176.0, 175.6, 171.6, 170.9, 170.6, 170.5, 169.3, 164.6, 161.4, 159.3, 157.1, 156.5, 153.5, 152.5, 151.8, 151.1, 146.4, 144.9, 141.7, 138.6, 138.4, 136.9, 134.5, 134.4, 133.9, 130.8, 129.8, 129.7, 129.4, 128.6, 128.5, 128.3, 127.7, 127.3, 125.9, 125.5, 122.5, 122.1, 120.1, 119.4, 118.0, 116.9, 109.6, 109.0, 108.7, 104.5, 104.4, 103.2, 99.9, 78.4, 74.3, 73.3, 72.1, 71.5, 66.2, 63.7, 61.9, 60.6 56.9, 56.1, 55.8, 55.4, 37.2, 33.3, 32.0, 29.6, 29.4, 26.1, 22.9 and 14.4; and

(h) pK_a values in acetonitrile:water (3:7) as follows: 3.0, 4.3, 7.4, 8.5, 9.9 and 10.9 pK_a values above 10.9 not determined.

4. An antibiotic compound represented by the structural formula (I)



(I)

wherein R_1 is hydrogen and R_2 is a glycolipid radical of unknown structure having an empirical formula $C_{17}H_{30}NO_6$ has the following characteristics:

(a) a white solid which decomposes at 250—300°C;

(b) an empirical formula $C_{76}H_{74}N_8O_{25}Cl_4$;

(c) an approximate elemental composition of 48.98 percent carbon, 4.56 percent hydrogen, 5.64 percent nitrogen and 8.29 percent chlorine when the water content was 6.9 percent;

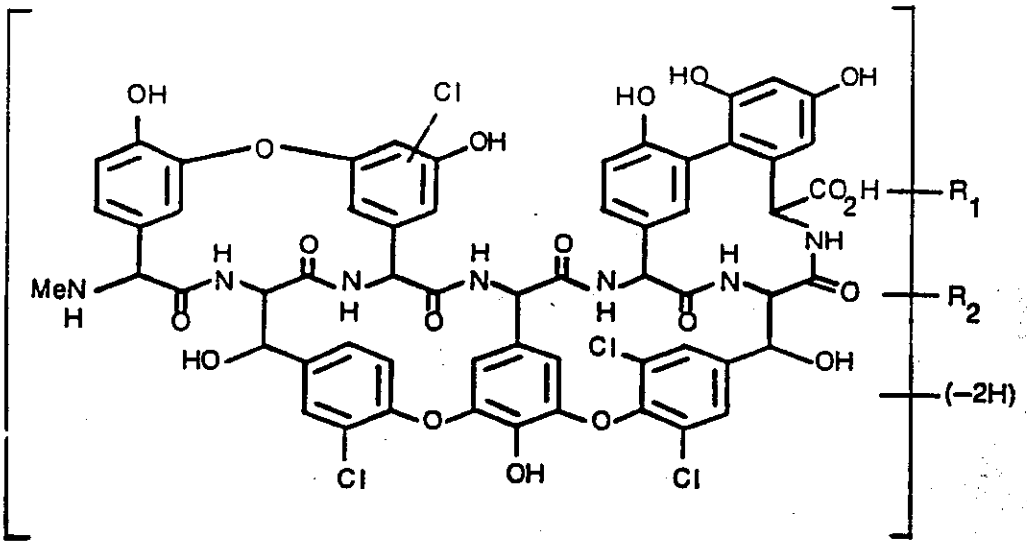
(d) an infrared absorption spectrum in potassium bromide which exhibits peaks at the following wave numbers in cm^{-1}: 3400, 2920, 1660, 1590, 1500, 1480, 1430, 1300, 1240, 1150, 1080, 1060 and 1010;

(e) a fast atom bombardment (FAB) mass spectrum with M + H at 1639 (major cluster);

(f) an ultraviolet spectrum in acetonitrile:water (1:1) which exhibits an absorption maximum at 281 nm under acidic conditions with an $E_{1\%}$ = 61.8 and at 303 nm under bascic conditions with an $E_{1\%}$ = 88;

(g) a carbon magnetic resonance spectrum at 90.56 MHz in $CD_3OD:D_2O$ (1:9) at a pH of 9.4 which exhibits the following chemical shifts in parts per million (ppm) relative to TMS as standard: 178.3, 177.6, 175.9, 175.6, 171.5, 171.0, 170.7, 170.3, 169.4, 164.0, 159.3, 158.9, 156.4, 152.5, 151.7, 151.1, 146.2, 144.7, 141.8, 138.7, 138.6, 136.8, 134.4, 133.8, 130.9, 129.8, 129.5, 128.6, 128.4, 127.9, 127.3, 126.0, 125.8, 122.5, 119.9, 119.3, 118.2, 116.9, 109.3, 108.8, 104.3, 104.2, 103.0, 99.4, 78.7, 74.4, 73.5, 72.1, 71.6, 65.8, 63.8, 62.5, 60.6, 57.1, 56.1, 55.9, 55.4, 39.7, 33.1, 30.3, 29.9, 29.7, 28.5, 28.0, 26.3 and 23.4.

5. An antibiotic compound represented by the structural formula (I)



(I)

wherein R_1 is hydrogen and R_2 is a glycolipid radical of unknown structure having an empirical formula $C_{16}H_{32}NO_6$ has the following characteristics:

(a) a white solid which decomposes at 250—300°C;

(b) an empirical formula $C_{77}H_{78}N_8O_{25}Cl_4$;

(c) an approximate elemental composition of 47.58 percent carbon, 4.51 percent hydrogen, 5.33 percent nitrogen and 8.08 percent chlorine when the water content was 7.8 percent;

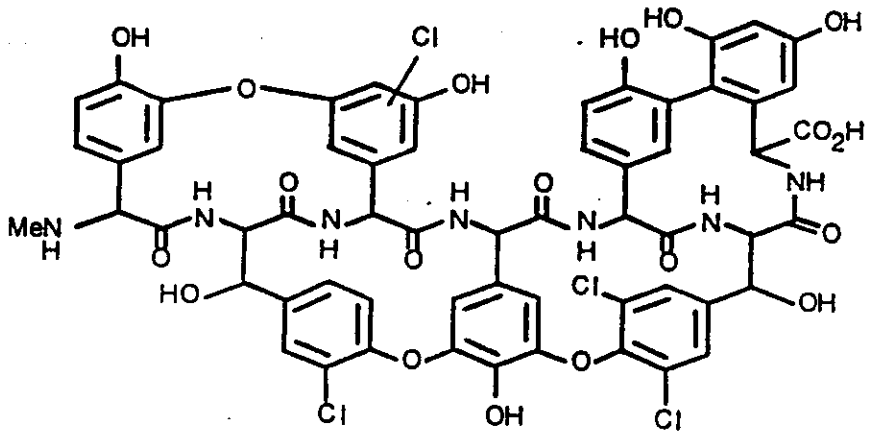
(d) an infrared absorption spectrum in potassium bromide which exhibits peaks at the following wave numbers in cm^{-1}: 3400, 2920, 1660, 1590, 1500, 1430, 1300, 1240, 1140, 1080, 1060 and 1010;

(e) a fast atom bombardment (FAB) mass spectrum with M + H at 1653 (major cluster);

(f) an ultraviolet spectrum in acetonitrile:water (1:1) which exhibits an absorption maximum at 281 nm under acidic conditions with an $E_{1\%}$ = 60.0 and at 303 nm under basic conditions with an $E_{1\%}$ = 83;

(g) a carbon magnetic resonance spectrum at 90.56 MHz in $CD_3OD:D_2O$ (1:9) at a pH of 9.4 which exhibits the following chemical shifts in parts per million (ppm) relative to TMS as standard: 178.1, 177.4, 175.5, 175.4, 171.4, 171.0, 170.7, 170.3, 169.3, 163.6, 159.1, 158.6, 156.5, 156.2, 152.7, 151.9, 151.8, 151.0, 146.2, 144.6, 142.0, 138.8, 138.6, 136.9, 134.8, 134.7, 134.0, 130.6, 129.9, 129.8, 129.4, 128.8, 128.3, 127.8, 127.5, 127.2, 126.4, 126.2, 125.8, 122.5, 122.0, 119.6, 119.1, 118.4, 116.9, 109.5, 109.2, 108.7, 104.2, 103.6, 99.8, 78.6, 74.6, 73.5, 72.1, 71.7, 66.0, 63.7, 62.1, 60.6, 56.9, 56.1, 55.9, 55.4, 39.6, 37.3, 33.2, 30.4, 30.0, 29.8, 28.5, 27.9, 26.3 and 23.1.

6. An antibiotic compound represented by the structural formula (II)



(II)

7. A process for the preparation of an antibiotic compound of Claim 1 which comprises the removal by acid hydrolysis of a glycolipid radical and/or a mannosyl radical from an antibiotic selected from the group consisting of AAD 216 complex, AAD 216A, AAD 216B, and AAD 216C.

8. A process for the preparation of the antibiotic compound of Claim 2 which comprises the removal by acid hydrolysis of a glycolipid radical from an antibiotic selected from the group consisting of AAD 216 complex, AAD 216A, AAD 216B and AAD 216B.

9. A process according to Claim 8 wherein the antibiotic hydrolyzed is AAD 216A, AAD 216B or AAD 216C.

10. A process according to Claim 9 wherein the hydrolysis is conducted in an aqueous organic solvent with 0.001 N hydrochloric acid at reflux.

11. A process for the preparation of the antibiotic compound of Claim 3 which comprises the removal by acid hydrolysis of a mannosyl radical from AAD 216A.

12. A process for the preparation of the antibiotic compound of Claim 4 which comprises the removal by acid hydrolysis of a mannosyl radical from AAD 216B.

13. A process for the preparation of the antibiotic compound of Claim 5 which comprises the removal by acid hydrolysis of a mannosyl radical from AAD 216C.

14. A process for the preparation of the antibiotic compound of Claim 6 which comprises the removal by acid hydrolysis of a glycolipid radical and a mannosyl radical from an antibiotic selected from the group consisting of AAD 216 complex, AAD 216A, AAD 216B, and AAD 216C.

15. A process according to Claim 14 wherein the antibiotic hydrolyzed is AAD 216A, AAD 216B or AAD 216C.

16. A process according to any one of Claims 11, 12, 13 or 15 wherein the hydrolysis is conducted in a polar organic solvent with 5% hydrochloric acid at elevated temperature.

17. A process according to any one of Claims 9, 11, 12, 13 or 15 wherein the antibiotic compound is isolated by chroamtographic means.

18. A composition comprising a product as defined in any one of Claims 1, 2, 3, 4, 5 or 6, or any mixture thereof, and a pharmaceutically acceptable carrier.

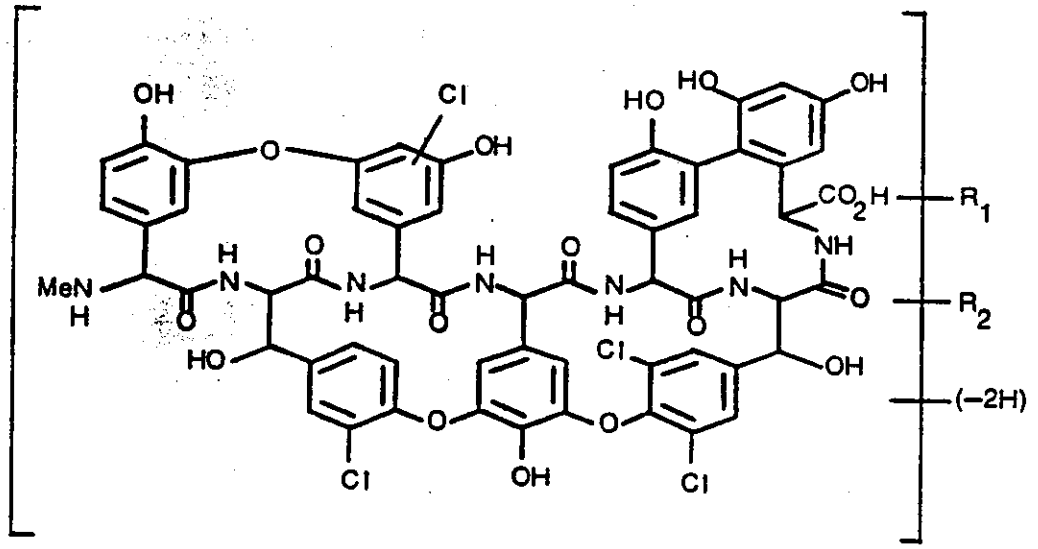
19. An animal feed composition supplemented by a nontoxic amount of a product as defined in any one of Claims 1, 2, 3, 4, 5 or 6, or any mixture thereof.

20. An animal feed premix composition comprising a premix vehicle and a product as defined in any one of Claims 1, 2, 3, 4, 5 or 6, or any mixture thereof.

21. A method for improving the growth rate and feed efficiency of meat or milk producing animals which comprises administering a product or composition as defined in any one of Claims 1, 2, 3, 4, 5, 6, 18, 19 or 20.

Claims for the Contracting State: AT

1. A process for preparing an antibiotic compound of the formula (I)



(I)

wherein R_1 is hydrogen or mannosyl and R_2 is hydrogen or a glycolipid radical of unknown structure with the proviso that at least one of R_1 and R_2 is hydrogen, which comprises:

i) for a compound wherein R_1 is hydrogen and R_2 is a glycolipid radical, de-mannosylating by hydrolysis AAD 216 complex, which is the compound of formula (I) wherein R_1 is mannosyl and R_2 is a glycolipid radical;

ii) for a compound wherein R_1 is mannosyl and R_2 is hydrogen, removing a glycolipid radical by hydrolysis from AAD 216 complex, which is the compound of formula (I) wherein R_1 is mannosyl and R_2 is a glycolipid radical;

and optionally thereafter forming a compound wherein R_1 and R_2 are both hydrogen by:

i) removing a glycolipid radical by hydrolysis from a compound wherein R_1 is hydrogen and R_2 is a glycolipid radical; or

ii) de-mannosylating by hydrolysis a compound wherein R_1 is mannosyl and R_2 is hydrogen.

2. The process for preparing a compound according to Claim 1 which comprises the removal by acid

hydrolysis of a glycolipid radical and/or a mannosyl radical from AAD 216 complex, AAD 216A, AAD 216B or AAD 216C.

3. The process according to Claim 1 for preparing AAD 216 pseudo-aglycone which comprises the removal by acid hydrolysis of a glycolipid radical from AAD 216 complex, AAD 216A, AAD 216B or AAD 216C.

4. The process according to Claim 1 for preparing AAD 216A pseudo-aglycone which comprises the removal by acid hydrolysis of a mannosyl radical from AAD 216A.

5. The process according to Claim 1 for preparing AAD 216B pseudo-aglycone which comprises the removal by acid hydrolysis of a mannosyl radical from AAD 216B.

6. The process according to Claim 1 for preparing AAD 216C pseudo-aglycone which comprises the removal by acid hydrolysis of a mannosyl radical from AAD 216C.

7. The process according to Claim 1 for preparing AAD 216 aglycone which comprises the removal by acid hydrolysis of a glycolipid radical and a mannosyl radical from AAD 216 complex, AAD 216A, AAD 216B or AAD 216C.

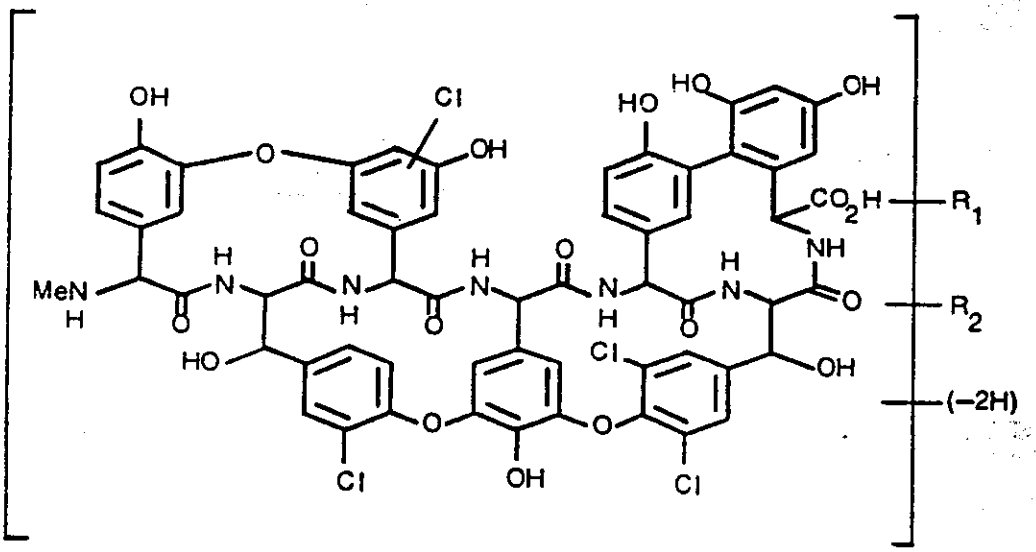
8. A process for preparing a composition comprising the admixing of AAD 216 aglycone, AAD 216 pseudo-aglycone, AAD 216A pseudo-aglycone, AAD 216B pseudo-aglycone, or AAD 216C pseudo-aglycone, or any mixture thereof, with a pharmaceutically acceptable carrier.

9. A process for preparing an animal feed composition comprising the admixing of AAD 216 aglycone, AAD 216 pseudo-aglycone, AAD 216A pseudo-aglycone, AAD 216B pseudo-aglycone or AAD 216C pseudo-aglycone, or any mixture thereof, with an animal feed.

10. A process for preparing an animal feed premix composition comprising the admixing of AAD 216 aglycone, AAD 216 pseudo-aglycone, AAD 216A pseudo-aglycone, AAD 216B pseudo-aglycone or AAD 216C pseudo-aglycone, or any mixture thereof with a premix vehicle.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

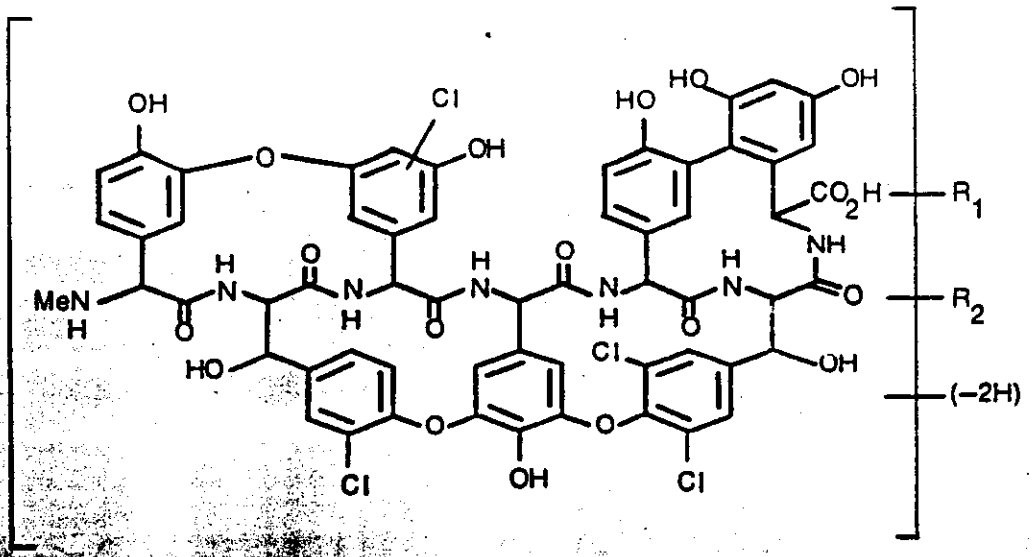
1. Antibiotikum der Strukturformel (I),



(I)

in der R_1 ein Wasserstoffatom oder ein Mannosylrest und R_2 ein Wasserstoffatom oder ein Glycolipidrest unbekannter Struktur ist, mit der Maßgabe, daß mindestens einer der beiden Reste R_1 und R_2 ein Wasserstoffatom ist, hergestellt durch saure hydrolytische Abspaltung eines Glycolipid- und/oder eines Mannosylrestes aus einem der Antibiotika AAD 216-Komplex, AAD 216A, AAD 216B oder AAD 216C.

2. Antibiotikum der Strukturformel (I),



(I)

in der R_1 ein Mannosylrest un R_2 ein Wasserstoffatom ist, mit den folgenden Merkmalen:

(a) blaßweiß-gelber Feststoff, der sich bei 300 bis 350°C zersetzt,

(b) empirische Formel: $C_{66}H_{66}N_7O_{24}Cl_4$,

(c) ungefähre Elementarzusammensetzung: von 47,54% Kohlenstoff, 4,00% Wasserstoff, 5,89% Stickstoff und 8,63% Chlor bei einem Wassergehalt von 12%,

(d) Infrarot-Absorptionsspektrum in Kaliumbromid mit Peaks bei folgenden Wellenzahlen (in cm^{-1}): 3400, 1660, 1610, 1590, 1510, 1460, 1430, 1390, 1300, 1230, 1180, 1150, 1120, 1060, 1010, 970 und 810;

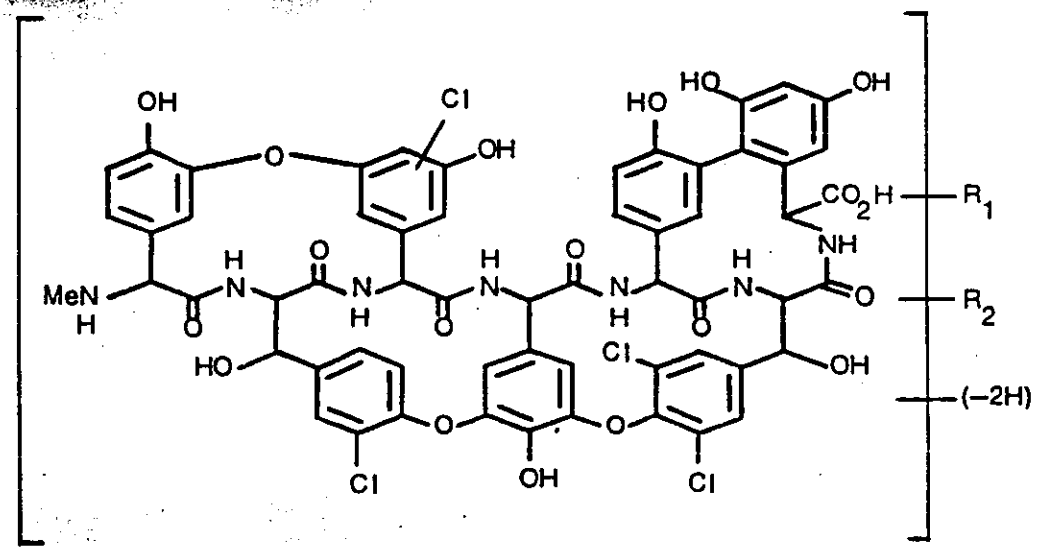
(e) FAB (fast atom bombardment)-Massenspektrum mit einem M+H-Signal bei 1458 (Haupt-Cluster);

(f) Ultraviolett-Spektrum in Acetonitril:Wasser (1:1), mit einem Absorptionsmaximum bei 281 nm mit $E_{1\%}$ = 79,7 unter sauren und einem Absorptionsmaximum bei 300 nm mit $E_{1\%}$ = 136 unter basischen Bedingungen;

(g) 90,56 MHz Kohlenstoff-Kernmagnetisches Resonanzspektrum in $CD_3OD:D_2O$ (1:9) bei pH 8,7 mit folgenden chemischen Verschiebungen (in parts per million, ppm) relativ zum TMS-Standard: 177,9, 174,6, 171,7, 170,9, 170,0, 169,2, 162,3, 158,8, 157,9, 155,2, 155,1, 153,9, 151,9, 149,7, 147,6, 147,2, 144,4, 141,0, 139,0 138,8, 137,5, 136,1, 134,6, 130,7, 130,0, 129,8, 129,2, 128,9, 128,7, 127,5, 127,3, 126,9, 126,4, 126,0, 125,2, 122,7, 122,2, 121,1, 119,9, 119,7, 118,4, 116,6, 110,7, 110,4, 108,5, 104,4, 103,3, 100,5, 98,1, 74,0, 72,1, 71,6, 71,4, 70,8, 67,4, 65,8, 63,7, 62,2, 61,6, 60,2, 56,0, 55,9, 55,0 und 32,9

(h) pK_a-Werte in Acetonitril:Wasser (3:7): 3,3, 7,1, 8,3, 9,1, 10,0 und 11,2 (pK_a-Werte über 11,2 wurden bestimmt).

3. Antibiotikum der Strukturformel (I),



(I)

in der R_1 ein Wasserstoffatom und R_2 ein Glycolipidrest unbekannter Struktur mit der empirischen Formel $C_{16}H_{20}NO_6$ ist, das die folgenden Mekmale aufweist:

(a) blaßweiß-gelber Feststoff, der sich bei 300 bis 350°C zersetzt;

(b) empirische Formel: $C_{75}H_{72}N_8O_{25}Cl_4$;

(c) ungefähre Elementarzusammensetzung: 49,76% Kohlenstoff, 4,51% Wasserstoff, 5,99% Stickstoff und 8,19% Chlor bei einem Wassergehalt von 9,4%;

(d) Infrarot-Absorptionsspektrum in Kaliumbromid mit Peaks bei den folgenden Wellenzahlen (in cm^{-1}): 3400, 2920, 1660, 1590, 1500, 1460, 1430, 1300, 1240, 1140, 1080, 1060 und 1010;

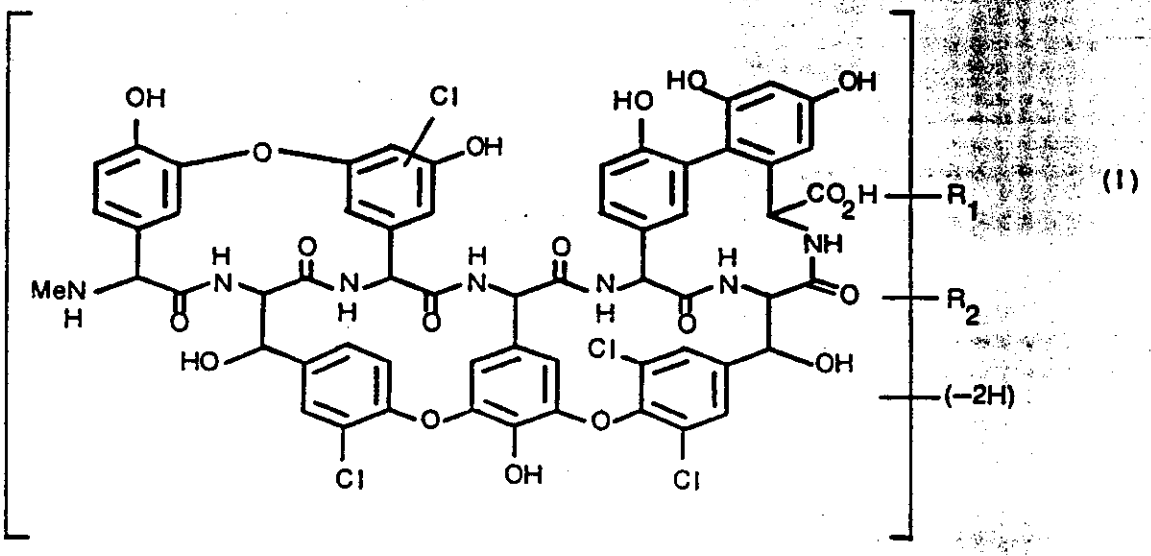
(e) FAB (fast atom bombardment)-Massenspektrum mit einem M+H-Signal bei 1625 (Haupt-Cluster);

(f) Ultraviolett-Spektrum in Acetonitril:Wasser (1:1), mit einem Absorptionsmaximum bei 281 nm mit $E_{1\%}$ = 63,2 unter sauren und einem Absorptionsmaximum bei 302 nm mit $E_{1\%}$ = 94 unter basischen Bedingungen;

(g) 90,56 MHz Kohlenstoff-Kernmagnetisches Resonanspektrum in $CD_3OD:D_2O$ (1:9) bei pH 9,4 mit folgenden chemischen Verschiebungen (in parts per million, ppm) relativ zum TMS-Standard: 178,2, 178,0, 176,0, 175,6, 171,6, 170,9, 170,6, 170,5, 169,3, 164,6, 161,4, 159,3, 157,1, 156,5, 153,5, 152,5, 151,8, 151,1, 146,4, 144,9, 141,7, 138,6, 138,4, 136,9, 134,5, 134,4, 133,9, 130,8, 129,8, 129,7, 129,4, 128,6, 128,5, 128,3, 127,7, 127,3, 125,9, 125,7, 125,5, 122,5, 122,1, 120,1, 119,4, 118,0, 116,9, 109,6, 109,0, 108,7, 104,5, 104,4, 103,2, 98,9, 78,4, 74,3, 73,3, 72,1, 71,5, 66,2, 63,7, 61,9, 60,6, 56,9, 56,1, 55,8, 55,4, 37,2, 33,3, 32,0, 29,6, 29,4, 26,1, 22,9 und 14,4; und

(h) pK_a-Werte in Acetonitril:Wasser (3:7): 3,0, 4,3, 7,4, 8,5, 9,9 und 10,9 (pK_a-Werte über 10,9 wurden nicht bestimmt).

4. Antibiotikum der Strukturformel (I);



in der R_1 ein Wasserstoffatom und R_2 ein Glycolipidrest unbekannter Struktur mit der empirischen Formel $C_{17}H_{30}NO_8$ ist, das die folgenden Merkmale aufweist:

(a) weißer Feststoff, der sich bei 250 bis 300°C zersetzt;

(b) empirische Formel: $C_{76}H_{74}N_8O_{25}Cl_4$;

(c) ungefähre Elementarzusammensetzung: 48,98% Kohlenstoff, 4,56% Wasserstoff, 5,64% Stickstoff und 8,29% Chlor bei einem Wassergehalt von 6,9%;

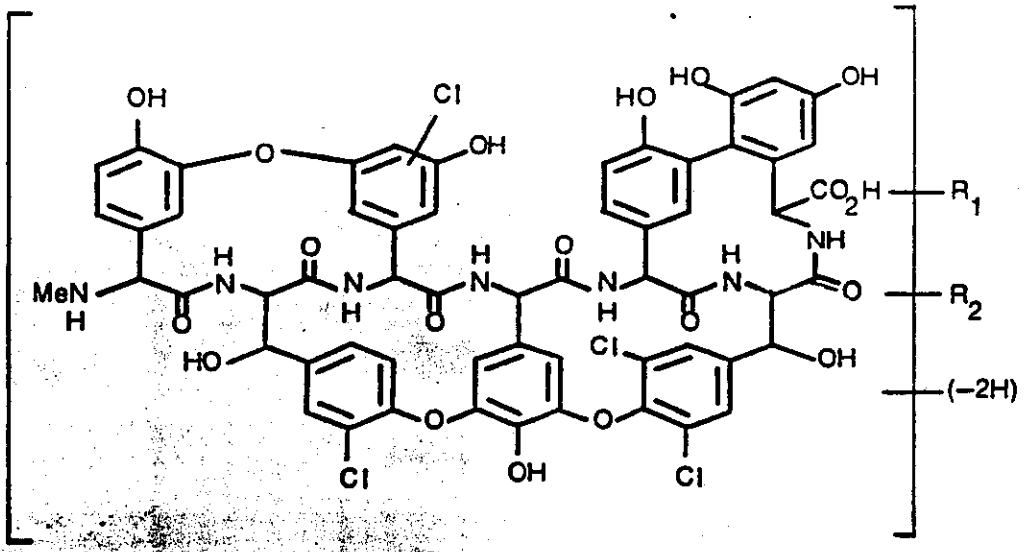
(d) Infrarot-Absorptionsspektrum in Kaliumbromid mit Peaks bei folgenden Welenzahlen (in cm^{-1}): 3400, 2920, 1660, 1590, 1500, 1480, 1430, 1300, 1240, 1150, 1080, 1060 und 1010;

(e) FAB (fast atom bombardment)-Massenspektrum mit einem M+H-Signal bei 1639 (Haupt-Cluster);

(f) Ultraviolett-Spektrum in Acetonitril:Wasser (1:1) mit einem Absorptionsmaximum bei 281 nm mit $E_{1\%}$ = 61,8 unter sauren und einem Absorptionsmaximum bei 303 nm mit $E_{1\%}$ = 88 unter basischen Bedingungen;

(g) 90,56 MHz Kohlenstoff-Kernmagnetisches Resonanzspektrum in $CD_3OD:D_2O$ (1:9) bei pH 9,4 mit folgenden chemischen Verschiebungen (in parts per million, ppm) relativ zum TMS-Standard: 178,3, 177,6, 175,9, 175,6, 171,5, 171,0, 170,7, 170,3, 169,4, 164,0, 159,3, 158,9, 156,4, 152,5, 151,7, 151,1, 146,2, 144,7, 141,8, 138,7, 138,6, 136,8, 134,4, 133,8, 130,9, 129,8, 129,5, 128,6, 128,4, 127,9, 127,3, 126,0, 125,8, 122,5, 119,9, 119,3, 118,2 116,9, 109,3, 108,8, 104,3, 104,2, 103,0, 99,4, 78,7, 74,4, 73,5, 72,1, 71,6, 65,8, 63,8, 62,5, 60,6, 57,1, 56,1, 55,9, 55,4, 39,7, 37,3, 33,1, 30,3, 29,9, 29,7, 28,5, 28,0, 26,3 und 23,4.

5. Antibiotikum der Strukturformel (I),



(I)

in der R_1 ein Wasserstoffatom und R_2 ein Glycolipidrest unbekannter Struktur mit der empirischen Formel $C_{18}H_{32}NO_6$ ist, das die folgenden Merkmale aufweist:

(a) weißer Feststoff, der sich bei 250 bis 300°C zersetzt;

(b) empirische Formel: $C_{77}H_{76}N_8O_{25}Cl_4$;

(c) ungefähre Elementarzusammensetzung: 47,58% Kohlenstoff, 4,51% Waserstoff, 5,33% Stickstoff und 8,08% Chlor bei einem Wassergehalt von 7,8%.

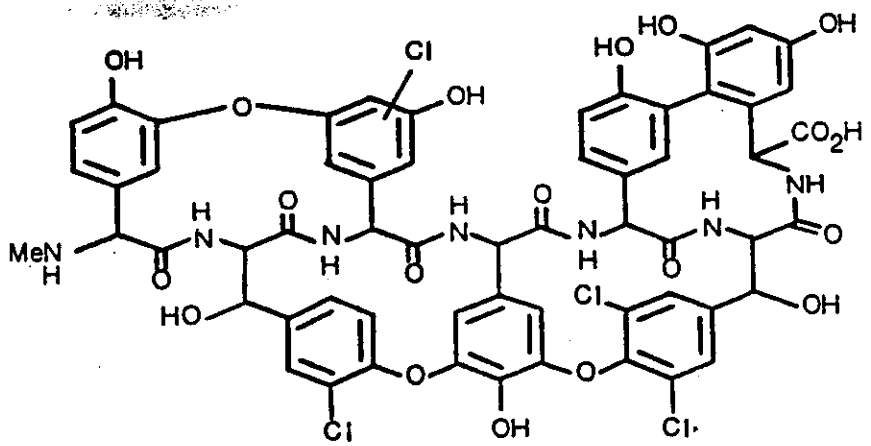
(d) Infrarot-Absorptionsspektrum in Kaliumbromid mit Peaks bei den folgenden Wellenzahlen (in cm^{-1}): 3400, 2920, 1660, 1590, 1550, 1430, 1300, 1240, 1140, 1080, 1060 und 1010;

(e) FAB (fast atom bombardment)-Massenspektrum mit einem M+H-Signal bei 1653 (Haupt-Cluster);

(f) Ultraviolett-Spektrum in Acetonitril:Wasser (1:1) mit einem Absorptionsmaximum bei 281 nm mit $E_{1\%}$ = 60,0 unter sauren und einem Absorptionsmaximum bei 303 nm mit $E_{1\%}$ = 83 unter basischen Bedingungen;

(g) 90,56 MHz Kohlenstoff-Kernmagnetisches Resonanzspektrum in $CD_3OD:D_2O$ (1:9) bei pH 9,4 mit folgenden chemischen Verschiebungen (in parts per million, ppm) relativ zum TMS-Standard: 178,1, 177,4, 175,5, 175,4, 171,4, 171, 0, 170,7, 170,3, 169,3, 163,6, 159,1, 158,6, 156,5, 156,2, 152,7, 151,9, 151,8, 151,0, 146,2, 144,6, 142,0, 138,8, 138,6, 136,9, 134,8, 134,7, 134,0, 130,6, 129,9, 129,8, 129,4, 128,8, 128,3, 127,8, 127,5, 127,2, 126,4, 126,2, 125,8, 122,5, 122,0, 119,6, 119,1, 118,4, 116,9, 109,5, 109,2, 108,7, 104,2, 103,6, 99,8, 78,6, 74,6, 73,5, 72,1, 71,7, 66,0, 63,7, 62,1, 60,6, 56,9, 56,1, 55,9, 55,4, 39,6, 37,3, 33,2, 30,4, 30,0, 29,8, 28,5, 27,9, 26,3 und 23,1.

6. Antibiotikum der Formel (II),



(II)

7. Verfahren zur Herstellung eines Antibiotikums nach Anspruch 1, umfassend die Abspaltung durch saure Hydrolyse eines Glycolipid- und/oder eines Mannosylrestes von einem der Antibiotika AAD 216-Komplex, AAD 216A, AAD 216B oder AAD 216C.

8. Verfahren zur Herstellung eines Antibiotikums nach Anspruch 2, umfassend die Abspaltung durch saure Hydrolyse eines Glycolipidrestes von einem der Antibiotika AAD 216-Komplex, AAD 216A, AAD 216B oder AAD 216C.

9. Verfahren nach Anspruch 8, bei dem das hydrolysierte Antibiotikum AAD 216, AAD 216B oder AAD 216C ist.

10. Verfahren nach Anspruch 9, bei dem die Hydrolyse in einem wäßrigen organischen Lösungsmittel mit 0,001 N Salzsäure unter Rückfluß durchgeführt wird.

11. Verfahren zur Herstellung des Antibiotikums nach Anspruch 3, bei dem ein Mannosylrest von AAD 216A durch saure Hydrolyse abgespalten wird.

12. Verfahren zur Herstellung des Antibiotikums nach Anspruch 4, bei dem ein Mannosylrest von AAD 216B durch saure Hydrolyse abgespalten wird.

13. Verfahren zur Herstellung des Antibiotikums nach Anspruch 5, bei dem ein Mannosylrest von AAD 216C durch saure Hydrolyse abgespalten wird.

14. Verfahren zur Herstellung des Antibiotikums nach Anspruch 6, bei dem ein Glycolipid- und ein Mannosylrest von einem Antibiotika AAD 216-Komplex, AAD 216A, AAD 216B oder AAD 216C durch saure Hydrolyse abgespalten werden.

15. Verfahren Anspruch 14, bei dem das hydrolysierte Antibiotikum AAD 216A, AAD 216B oder AAD 216C ist.

16. Verfahren nach einem der Ansprüche 11, 12, 13 oder 15, bei dem die Hydrolyse in einem polaren organischen Lösungsmittel mit 5% Salzsäure bei erhöhter Temperatur durchgeführt wird.

17. Verfahren nach einem der Ansprüche 9, 11, 12, 13 oder 15, bei dem das Antibiotikum auf chromatographischem Wege isoliert wird.

18. Zusammensetzung, umfassend ein Produkt nach einem der Ansprüche 1 bis 6 oder ein Gemisch dieser Produkte und einen pharmazeutisch verträglichen Träger.

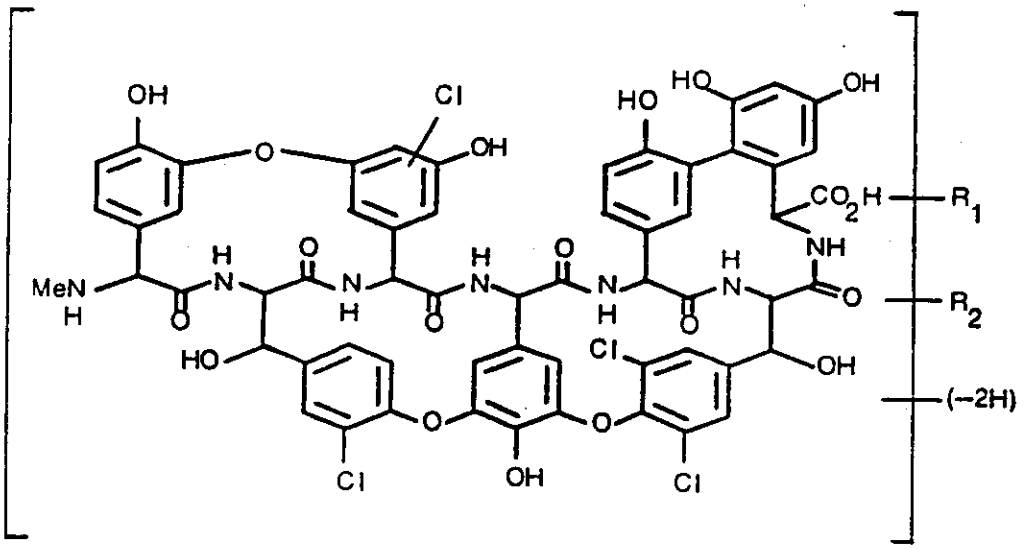
19. Tierfuttermittel, ergänzt mit einer nicht-toxischen Menge eines Produktes nach einem der Ansprüche 1 bis 6 oder mit einem Gemisch dieser Produkte.

20. Vorgemischtes Tierfuttermittel, umfassend vorgemischte Hilfsstoffe und ein Produkt nach einem der Ansprüche 1 bis 6 oder ein Gemisch dieser Produkte.

21. Verfahren zur Verbesserung der Wachstumsgeschwindigkeit und der Futterverwertung von Fleisch oder Milch produzierenden Tieren, umfassend die Verabreichung eines Produkts oder einer Zusammensetzung nach einem der Ansprüche 1 bis 6, 18, 19 oder 20.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung eines Antibiotikums der Formel (I)



(I)

in der R_1 ein Wasserstoffatom oder ein Mannosylrest und R_2 ein Wasserstoffatom oder ein Glycolipidrest unbekannter Struktur ist, mit der Maßgabe, daß mindestens einer der beiden Reste R_1 und R_2 ein Wasserstoffatom ist, umfassend:

i) für eine Verbindung, in der R_1 ein Wasserstoffatom und R_2 ein Glycolipidrest ist, die hydrolytische Demannosylierung des AAD 216-Komplexes, welcher die Verbindung der allgemeinen Formel I ist, in der R_1 ein Mannosyl- und R_2 ein Glycolipidrest ist,

ii) für eine Verbindung, in der R_1 ein Mannosylrest und R_2 ein Wasserstoffatom ist, die hydrolytische Abspaltung eines Glycolipidrestes aus dem AAD 216-Komplex, welcher die Verbindung der allgemeinen Formel I ist, in der R_1 ein Mannosyl- und R_2 ein Glycolipidrest ist,

und gegebenenfalls danach Erzeugung einer Verbindung, in der sowohl R_1 als auch R_2 Wasserstoffatome sind, durch

i) hydrolytische Abspaltung eines Glycolipidrestes aus einer Verbindung, in der R_1 ein Wasserstoffatom und R_2 ein Glycolipidrest ist oder

ii) hydrolytische Demannosylierung einer Verbindung, in der R_1 ein Mannosylrest und R_2 ein Wasserstoffatom ist.

2. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, umfassend die Abspaltung eines Glycolipid- und/oder eines Mannosylrest vom AAD 216-Komplex, AAD 216A, AAD 216B oder AAD 216C durch saure Hydrolyse.

3. Verfahren nach Anspruch 1 zur Herstellung von AAD 216 Pseudoaglycon, umfassend die Abspaltung eines Glycolipidrestes vom AAD 216-Komplex, AAD 216A, AAD 216B oder AAD 216C durch saure Hydrolyse.

4. Verfahren nach Anspruch 1 zur Herstellung von AAD 216A Pseudoaglycon, umfassend die Abspaltung eines Mannosylrestes von AAD 216A durch saure Hydrolyse.

5. Verfahren nach Anspruch 1 zur Herstellung von AAD 216B Pseudoaglycon, umfassend die Abspaltung eines Mannosylrestes von AAD 216B durch saure Hydrolyse.

6. Verfahren nach Anspruch 1 zur Herstellung von AAD 216C Pseudoaglycon, umfassend die Abspaltung eines Mannosylrestes von AAD 216C durch saure Hydrolyse.

7. Verfahren nach Anspruch 1 zur Herstellung von AAD 216 Aglycon, umfassend die Abspaltung eines Glycolipid- und eines Mannosylrestes vom AAD 216-Komplex, AAD 216A, AAD 216B oder AAD 216C durch saure Hydrolyse.

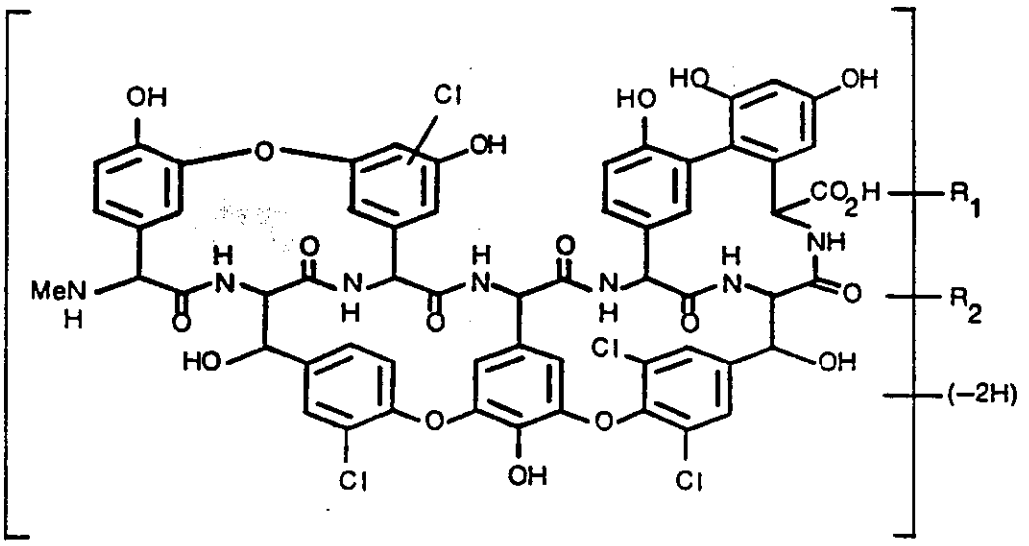
8. Verfahre zur Herstellung einer Zusammensetzung, umfassend das Vermischen von AAD 216 Aglycon, AAD 216 Pseudoaglycon, AAD 216A Pseudoaglycon, AAD 216B Pseudoaglycon oder AAD 216C Pseudoaglycon oder irgendeines Gemisches dieser Stoffe mit einem pharmazeutisch verträglichen Trägermaterial.

9. Verfahren zur Herstellung eines Tierfuttermittels, umfassend das Vermischen von AAD 216 Aglycon, AAD 216 Pseudoaglycon, AAD 216A Pseudoaglycon, AAD 216B Pseudoaglycon oder AAD 216C Pseudoaglycon oder irgendeines Gemisches dieser Stoffe mit einem Tierfutter.

10. Verfahren zur Herstellung eines vorgemischten Tierfuttermittels, umfassend das Vrmischen von AAD 216 Aglycon, AAD 216 Pseudoaglycon, AAD 216A Pseudoaglycon, AAD 216B Pseudoaglycon oder AAD 216C Pseudoaglycon oder irgendeines Gemisches dieser Stoffe mit vorgemischten Hilfsstoffen.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

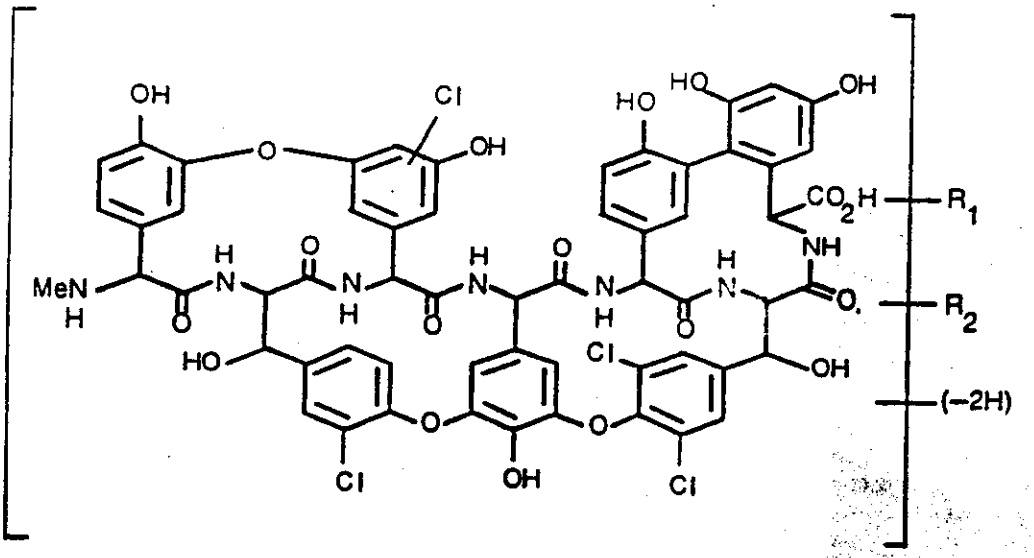
1. Composé antibiotique représenté par la formule de structure (I):



(I)

dans laquelle R_1 est de l'hydrogène ou mannosyle et R_2 est de l'hydrogène ou un radical glycolipidique de structure inconnue à la condition que au moins un des R_1 et R_2 soit de l'hydrogène, préparé par l'élimination par hydrolyse acide d'un radical glycolipidique et/ou d'un radical mannosyle d'un antibiotique choisi dans le groupe composé par le complexe AAD 216, l'AAD 216A, l'AAD 216B et l'AAD 216C.

2. Composé antibiotique représenté par la formule de structure (I):



(I)

dans laquelle R^1 est mannosyle et R_2 est de l'hydrogène ayant les caractéristiques suivantes:

(a) solide blanc-jaune pâle qui se décompose à 300—350°C;

(b) une formule empirique $C_{65}H_{55}N_7O_{24}Cl_4$;

(c) une composition élémentaire approximative de 47,54 pourcent de carbone, 4,00 pourcent d'hydrogène, 5,89 pourcent d'azote et 8,63 pourcent de chlore lorsque la teneur en eau est de 12 pourcent;

(d) un spectre d'absorption infrarouge dans le bromure de potassium qui présente des pics aux nombres d'ondes suivants en cm^{-1}: 3400, 1660, 1610, 1590, 1510, 1460, 1430, 1390, 1300, 1230, 1180, 1150, 1120, 1060, 1010, 970 et 810;

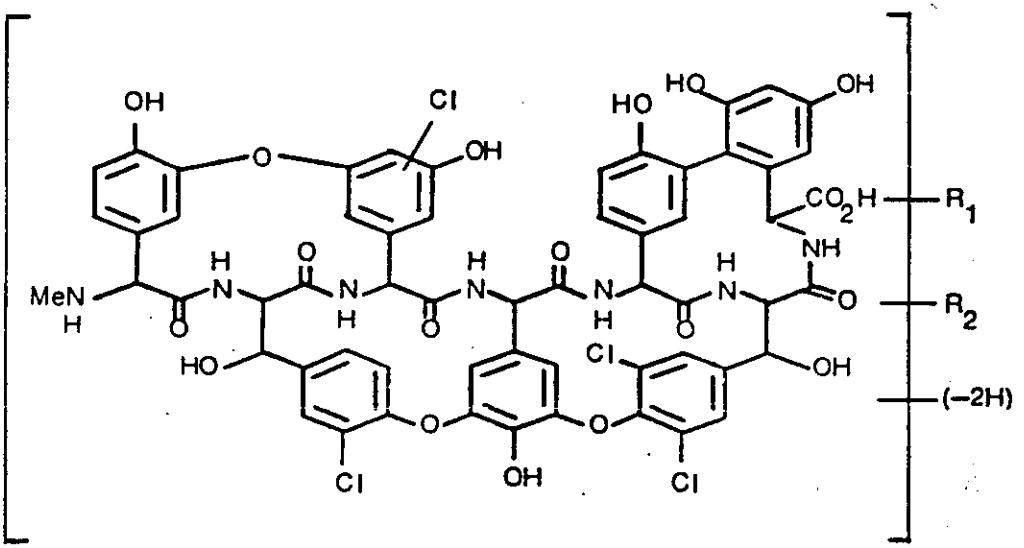
(e) un spectre de masse par bombardement atomique rapide (FAB) avec M+H à 1458 (groupement principal);

(f) un spectre ultraviolet dans le mélange acétonitrile:eau (1:1) qui présente un maximum d'absorption à 281 nm dans des conditions acides avec un $E_{1\%}$ = 79,7 et à 300 nm dans des conditions basiques avec un $E_{1\%}$ = 136;

(g) un spectre de résonance magnétique du carbone à 90,56 MHz dans le mélange $CD_3OD:D_2O$ (1:9) à un pH de 8,7 qui présente les glissements chimiques suivants en partie par million (ppm) par rapport à TMS comme standard: 177,9, 174,6, 171,7, 170,9, 170,0, 169,2, 162,3, 158,8, 157,9, 155,2, 155,1, 153,9, 151,9, 149,7, 147,6, 147,2, 144,4, 141,0, 139,0 138,8, 137,5, 136,1, 134,6, 130,7, 130,0, 129,8, 129,2, 128,9, 128,7, 127,5, 127,3, 126,9, 126,4, 126,0, 125,2, 122,7, 122,2, 121,1, 119,9, 119,7, 118,4, 116,6, 110,7, 110,4, 108,5, 104,4, 103,3, 100,5, 98,1, 74,0, 72,1, 71,6, 71,4, 70,8, 67,4, 65,8, 63,7, 62,2, 61,6, 60,2, 56,0, 55,9, 55,0 et 32,9 et

(h) des valeurs pK_a dans le mélange acétonitrile:eau (3:7) comme suit: 3,3, 7,1, 8,3, 9,1, 10,0 et 11,2, les valeurs pK_a au dessus de 11,2 n'étant pas déterminées.

3. Composé antibiotique représenté par la formule de structure (I):



(I)

dans laquelle R_1 est de l'hydrogène et R_2 est un glycolipide de structure inconnue de formule empirique $C_{16}H_{28}NO_6$ et ayant les caractéristiques suivantes:

(a) solide blanc-jaune pâle qui se décompose à 300—350°C;

(b) une formule empirique $C_{75}H_{72}N_8O_{25}Cl_4$;

(c) une composition élémentaire approximative de 49,76% de carbone, 4,51 pourcent d'hydrogène, 5,99 pourcent d'azote et 8,19 pourcent de chlore lorsque la teneur en eau est de 9,4 pourcent;

(d) un spectre d'absorption infrarouge dans le bromure de potassium qui présente des pics aux nombres d'ondes suivants en cm^{-1}: 3400, 2920, 1660, 1590, 1500, 1460, 1430, 1300, 1240, 1140, 1080, 1060 et 1010;

(e) un spectre de masse par bombardement atomique rapide (FAB) avec M+H à 1625 (groupement principal);

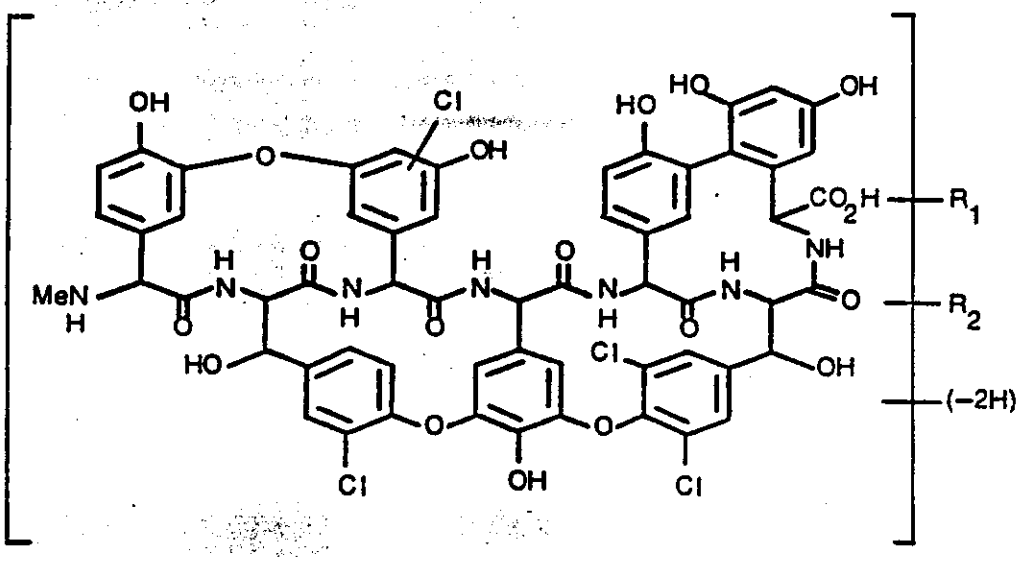
(f) un spectre ultraviolet dans le mélange acétonitrile:eau (1:1) qui présente un maximum d'absorption à 281 nm dans des conditions acides avec un $E_{1\%}$ = 63,2 et à 302 nm dans des conditions basiques avec un $E_{1\%}$ = 94;

(g) un spectre de résonance magnétique du carbone à 90,56 MHz dans le mélange $CD_3OD:D_2O$ (1:9) à un pH de 9,4 qui présente les glissements chimiques suivants en partie par million (ppm) par rapport à TMS comme standard:

178,2, 178,0, 176,0, 175,6, 171,6, 170,9, 170,6, 170,5, 169,3, 164,6, 161,4, 159,3, 157,1, 156,5, 153,5, 152,5, 151,8, 151,1, 146,4, 144,9, 141,7, 138,6, 138,4, 136,9, 134,5, 134,4, 133,9, 130,8, 129,8, 129,7, 129,4, 128,6, 128,5, 128,3, 127,7, 127,3, 125,9, 125,7, 125,5, 122,5, 122,1, 120,1, 119,4, 118,0, 116,9, 109,6, 109,0, 108,7, 104,5, 104,4, 103,2, 98,9, 78,4, 74,3, 73,3, 72,1, 71,5, 66,2, 63,7, 61,9, 60,6, 56,9, 56,1, 55,8, 55,4, 37,2, 33,3, 32,0, 29,6, 29,4, 26.1, 22,9 et 14,4 et

(h) des valeurs pK_a dans le mélange acétonitrile:eau (3:7) comme suit: 3,0, 4,3, 7,4, 8,5, 9,9 et 10,9, les valeurs pK_a au-dessus de 10,9 n'étant pas déterminées.

4. Composé antibiotique représenté par la formule de structure (I):



(I)

dans laquelle R_1 est de l'hydrogène et R_2 est un radical glycolipidique de structure inconnue de formule empirique $C_{17}H_{30}NO_6$ ayant les caractéristiques suivantes;

(a) solide blanc qui se décompose à 250—300°C;

(b) formule empirique $C_{78}H_{74}N_8O_{25}Cl_4$;

(c) une composition élémentaire approximative de 48,98 pourcent de carbone, 4,56 pourcent d'hydrogène, 5,64 pourcent d'azote et 8,29 pourcent de chlore lorsque la teneur en eau est de 6,9 pourcent;

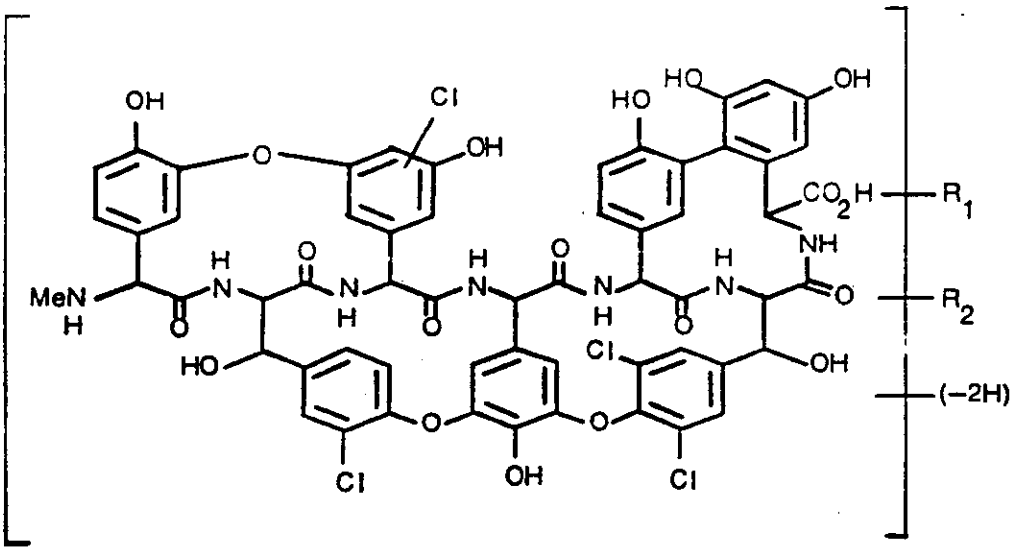
(d) un spectre d'absorption infrarouge dans le bromure de potassium qui présente des pics aux nombres d'ondes suivants en cm^{-1}: 3400, 2920, 1660, 1590, 1500, 1480, 1430, 1300, 1240, 1150, 1080, 1060 et 1010;

(e) un spectre de masse par bombardement atomique rapide (FAB) avec M+H à 1639 (groupement principal);

(f) un spectre ultraviolet dans le mélange acétonitrile:eau (1:1) qui présente un maximum d'absorption à 281 nm dans des conditions acides avec un $E_{1\%}$ = 61,8 et à 303 nm dans des conditions basiques avec un $E_{1\%}$ = 88;

(g) un spectre de résonance magnétique du carbone à 90,56 MHz dans le mélange $CD_3OD:D_2O$ (1:9) à un pH de 9,4 qui présente les glissements chimiques suivants en parties par million (ppm) par rapport à TMS comme standard: 178,3, 177,6, 175,9, 175,6, 171,5, 171,0, 170,7, 170,3, 169,4, 164,0, 159,3, 158,9, 156,4, 152,5, 151,7, 146,2, 144,7, 141,8, 138,7, 138,6, 136,8, 134,4, 133,8, 130,9, 129,8, 129,5, 128,6, 128,4, 127,9, 127,3, 126,0, 125,8, 122,5, 119,9, 119,3, 118,2 116,9, 109,3, 108,8, 104,3, 104,2, 103,0, 99,4, 78,7, 74,4, 73,5, 72,1, 71,6, 65,8, 63,8, 62,5, 60,6, 57,1, 56,1, 55,9, 55,4, 39,7, 37,3, 33,1, 30,3, 29,9, 29,7, 28,5, 28,0, 26,3 et 23,4.

5. Composé antibiotique représenté par la formule de structure (I):



(I)

dans laquelle R_1 est de l'hydrogène et R_2 est un radical glycolipidique de structure inconnue, de formule empirique $C_{18}H_{32}NO_6$ ayant les caractéristiques suivantes:

(a) solide blanc qui se décompose à 250—300°C;

(b) une formule empirique $C_{77}H_{76}N_8O_{25}Cl_4$;

(c) une composition élémentaire approximative de 47,58 pourcent de carbone, 4,51 pourcent d'hydrogène, 5,33 pourcent d'azote et 8,08 pourcent de chlore lorsque la teneur en eau est de 7,8 pourcent;

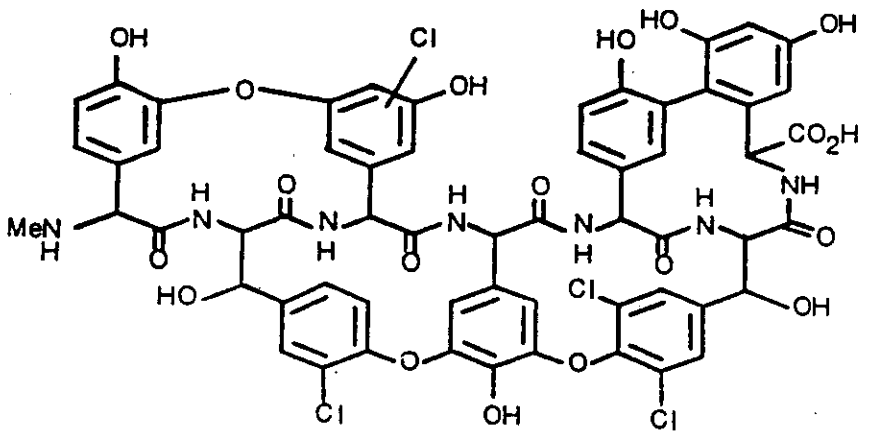
(d) un spectre d'absorption infrarouge dans le bromure de potassium qui présente des pics aux nombres d'ondes suivants en cm^{-1}: 3400, 2920, 1660, 1590, 1500, 1430, 1300, 1240, 1140, 1080, 1060 et 1010;

(e) un spectre de masse par bombarbement atomique rapide (FAB) avec M+H à 1653 (groupement principal);

(f) un spectre ultraviolet dans le mélange acétonitrile:eau (1:1) qui présente un maximum d'absorption à 281 nm dans des conditions acides avec un $E_{1\%}$ = 60,0 et à 303 nm dans des conditions basiques avec un $E_{1\%}$ = 83;

(g) un spectre de résonance magnétique du carbone à 90,56 MHz dans le mélange $CD_3OD:D_2O$ (1:9) à un pH de 9,4 qui présente les glissements chimiques suivants en parties par million (ppm) par rapport à TMS comme standard: 178,1, 177,4, 175,5, 175,4, 171,4, 171, 0, 170,7, 170,3, 169,3, 163,6, 159,1, 158,6, 156,5, 156,2, 152,7, 151,9, 151,8, 151,0, 146,2, 144,6, 142,0, 138,8, 138,6, 136,9, 134,8, 134,7, 134,0, 130,6, 129,9, 129,8, 129,4, 128,8, 128,3, 127,8, 127,5, 127,2, 126,4, 126,2, 125,8, 122,5, 122,0, 119,6, 119,1, 118,4, 116,9, 109,5, 109,2, 108,7, 104,2, 103,6, 99,8, 78,6, 74,6, 73,5, 72,1, 71,7, 66,0, 63,7, 62,1, 60,6, 56,9, 56,1, 55,9, 55,4, 39,6, 37,3, 33,2, 30,4, 30,0, 29,8, 28,5, 27,9, 26,3 et 23,1.

6. Composé antibiotique représenté par la formule de structure (II):



(II)

7. Procédé pour la préparation d'un composé antibiotique de la Revendication 1 qui comprend l'enlèvement par hydrolyse acide d'un radical glycolipidique et/ou d'un radical mannosyle d'un antibiotique choisi dans le groupe composé du complexe AAD 216, de l'AAD 216A, de l'AAD 216B et de l'AAD 216C.

8. Procédé pour la préparation du composé antibiotique de la Revendication 2 qui comprend l'enlèvement par hydrolyse acide d'un radical glycolipidique d'un antibiotique choisi dans le groupe composé du complexe AAD 216, de l'AAD 216A, de l'AAD 216B et de l'AAD 216C.

9. Procédé suivant la Revendication 8 dans laquelle l'antibiotique hydrolysé est l'AAD 216A, l'AAD 216B ou l'AAD 216C.

10. Procédé suivant la Revendication 9 dans laquelle l'hydrolyse est effectuée dans un solvant organique aqueux avec de l'acide chlorhydrique 0,001 N au reflux.

11. Procédé pour la préparation du composé antibiotique de la Revendication 3 qui comprend l'enlèvement d'un radical mannosyle de l'AAD 216A, par hydrolyse acide.

12. Procédé pour la préparation du composé antibiotique de la Revendication 4 qui comprend l'enlèvement d'un radical mannosyle de l'AAD 216B, par hydrolyse acide.

13. Procédé pour la préparation du composé antibiotique de la Revendication 5 qui comprend l'enlèvement d'un radical mannosyle de l'AAD 216C, par hydrolyse acide.

14. Procédé pour la préparation du composé antibiotique de la Revendication 6 qui comprend l'enlèvement, par hydrolyse acide, d'un radical glycolipidique et d'un radical mannosyle d'un antibiotique choisi dans le groupe composé du complexe AAD 216, de l'AAD 216A, de l'AAD 216B et de l'AAD 216C.

15. Procédé suivant la Revendication 14 dans laquelle l'antibiotique hydrolysé est l'AAD 216A, l'AAD 216B ou l'AAD 216C.

16. Procédé suivant l'une quelconque des Revendications 11, 12, 13 ou 15 dans laquelle l'hydrolyse est effectuée dans un solvant organique polaire avec de l'acide chlorhydrique à 5% à température élevée.

17. Procédé suivant l'une quelconque des Revendications 9, 11, 12, 13, ou 15 dans laquelle le composé antibiotique est isolé par des moyens chromatographiques.

18. Composition comprenant un produit tel que défini dans l'une quelconque des Revendications 1, 2, 3, 4, 5 ou 6 n'importe lequel de leurs mélanges et un support pharmaceutiquement acceptable.

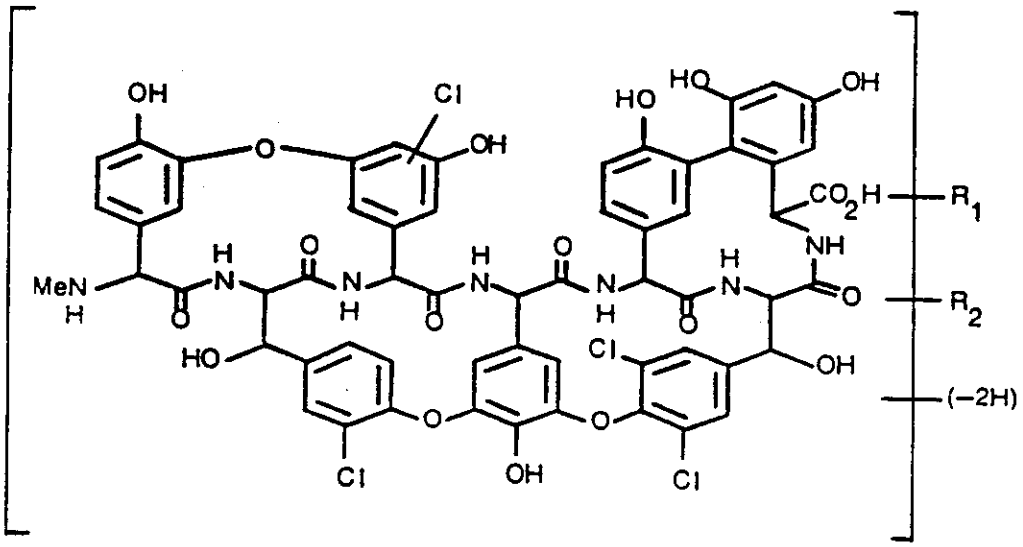
19. Composition alimentaire pour animaux additionnée d'une quantité non toxique d'un composé tel que défini dans l'une quelconque des Revendications 1, 2, 3, 4, 5 ou 6 ou de n'importe lequel de leurs mélanges.

20. Composition de prémélange pour aliment pour animaux comprenant un véhicule de prémélange et un produit tel que défini dans l'une quelconque des Revendications 1, 2, 3, 4, 5 ou 6 ou n'importe lequel de leurs mélanges.

21. Méthode pour améliorer la vitesse de croissance et l'efficacité alimentaire d'animaux producteurs de viande ou de lait qui comprend l'administration d'un produit ou d'une composition tels que définis dans l'une quelconque des revendications 1, 2, 3, 4, 5, 6, 18, 19 ou 20.

Revendications pour l'Etat contractant: AT

1. Procédé pour préparer un composé antibiotique de formule (I):



(I)

dans laquelle R_1 est de l'hydrogène ou mannosyle et R_2 est de l'hydrogène ou un radical glycolipidique de structure inconnue à la condition que au moins un des R_1 et R_2 soit de l'hydrogène, qui comprend:

i) pour un composé ou R_1 est de l'hydrogène et R_2 est un radical glycolipidique, la dé-mannosylation par hydrolyse du complexe AAD 216 qui est le composé de formule (I) dans laquelle R_1 est mannosyle et R_2 est un radical glycolipidique;

ii) pour un composé où R_1 est mannosyle et R_2 est de l'hydrogène, l'enlèvement d'un radical glycolipidique par hydrolyse du complexe AAD 216, qui est le composé de formule (I) dans laquelle R_1 est mannosyle et R_2 est un radical glycolipidique;

et, facultativement, la formation subséquente d'un composé où R_1 et R_2 sont tous deux de l'hydrogène par:

i) enlèvement d'un radical glycolipidique par hydrolyse d'un composé dans lequel R_1 est de l'hydrogène et R_2 est un radical glycolipidique; ou

ii) la dé-mannosylation par hydrolyse d'un composé dans lequel R_1 est mannosyle et R_2 est de l'hydrogène.

2. Procédé pour préparer un composé suivant la revendication 1 qui comprend l'enlèvement, par hydrolyse acide, d'un radical glycolipidique et/ou d'un radical mannosyle du complexe AAD 216, de l'AAD 216A, de l'AAD 216B ou de l'AAD 216C.

3. Procédé suivant la revendication 1 pour préparer la pseudo-aglycone d'AAD 216 qui comprend l'enlèvement, par hydrolyse acide, d'un radical glycolipidique du complexe AAD 216, de l'AAD 216A, de l'AAD 216B ou de l'AAD 216C.

4. Procédé suivant la revendication 1 pour préparer la pseudo-aglycone d'AAD 216A qui comprend l'enlèvement par hydrolyse acide, d'un radical mannosyle de l'AAD 216A.

5. Procédé suivant la revendication 1 pour préparer la pseudo-aglycone d'AAD 216B qui comprend l'enlèvement par hydrolyse acide d'un radical mannosyle de l'AAD 216B.

6. Procédé suivant la revendication 1 pour préparer la pseudo-aglycone d'AAD 216C qui comprend l'enlèvement, par hydrolyse acide, d'un radical manosyle de l'AAD 216C.

7. Procédé suivant la revendication 1 pour préparer la pseudo-aglycone de l'AAD 216 qui comprend l'enlèvement, par hydrolyse acide, d'un radical glycolipidique et d'un radical mannosyle du complexe AAD 216, de l'AAD 216A, de l'AAD 216B ou de l'AAD 216C.

8. Procédé pour préparer une composition comprenant le mélange d'aglycone de l'AAD 216, de pseudo-aglycone d'AAD 216, de pseudo-aglycone d'AAD 216A, de pseudo-aglycone d'AAD 216B ou de pseudo-aglycone d'AAD 216C ou n'importe lequel de leurs mélanges avec un support pharmaceutiquement acceptable.

9. Procédé pour préparer une composition alimentaire pour aimaux comprenant le mélange d'aglycone d'AAD 216, de pseudo-aglycone d'AAD 216, de pseudo-aglycone d'AAD 216A, de pseudo-aglycone d'AAD 216B ou de pseudo-aglycone d'AAD 216C ou de n'importe lequel de leurs mélanges, avec un aliment pour animaux.

10. Procédé pour préparer une composition de prémélange pour aliment pour animaux comprenant le mélange d'aglycone d'AAD 216, de pseudo-aglycone d'AAD 216, de pseudo-aglycone d'AAD 216A, de pseudo-aglycone d'AAD 216B ou de pseudo-aglycone d'AAD 216C ou n'importe lequel de leurs mélanges avec un support de prémélange.

REGISTER ENTRY FOR EP0132116

European Application No EP84304733.3 filing date 11.07.1984

Priorities claimed:
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17.05.1984 in United States of America - doc: 611070

Designated States BE CH DE FR GB IT LI LU NL SE AT

Title THE AGLYCONE AND PSEUDO-AGLYCONES OF THE AAD 216 ANTIBIOTICS

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Classified to
C3H U1S
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