Kirk-Othmer Encyclopedia of Chemical Technology.

GLYCOPEPTIDES (DALBAHEPTIDES)

The vancomycin–ristocetin family of glycopeptides (1, 2) is a subclass of linear sugar-containing peptides composed of seven amino acids cross-linked to generate a specific stereochemical configuration. This configuration forms the basis of a particular mechanism of action, eg, complexation with the D-alanyl-D-alanine terminus of bacterial cell wall components (3, 4). Because the mechanism of action is the distinguishing feature of these peptides, the term dalbaheptide, from D-al(anyl-D-alanine)b(inding)a(ntibiotics) having hept(apept)ide structure, has been proposed to distinguish them within the larger and diverse groups of glycopeptide antibiotics (5).

About 40 different naturally produced dalbaheptides have been reported (Table 1), which correspond to a larger number of chemical entities (Tables 2, 3, 4, 5, 6). Many of these antibiotics are groups of strictly related factors called complexes. Among them, vancomycin (**39**) (Table 4) (6) and the teicoplanins (**18–22**) (Table 3) (7) are used clinically as a result of high activity against gram-positive pathogens such as many coagulase-negative *Staphylococci* (CNS), *corynebacteria*, *Clostridium difficile*, multiresistant *Staphylococcus aureus*, and highly gentamicin-resistant *Enterococci* which are refractory to established drugs. Eremomycin (**52**) (Table 4) is under clinical evaluation (8). Many patents claim feed-utilization efficiency increase and growth promotion in domestic animals for several dalbaheptides but only avoparcin (**63**) (Avotan) (Table 5) is commercially used. The platelet aggregation ability of ristocetin A (**1**) (Table 2) renders it a suitable diagnostic agent for von Willebrand's disease, a hematologic disorder of genetic origin (9).

Knowledge of the mechanism of action and investigations on the physico-chemical characteristics of the therapeutically used dalbaheptides has stimulated the transformation of natural antibiotics into new derivatives using both chemical and biosynthetic modification.

1. Naturally Occurring Dalbaheptides

Vancomycin (**39**) was introduced into clinical practice much earlier than its structure was elucidated. Structure investigations lasted 25 years (10–12), the structure being definitely assigned in 1983 (13). Structure elucidation of new dalbaheptides is done much faster by the instrumental techniques utilized in the 1990s. Especially helpful are: hplc on new stationary phases (14) (see Chromatography); high field nmr including two-dimensional (2-D) experiments for structure elucidation (15, 59) (see Magnetic spin resonance); and soft ionization by fast atom bombardment mass spectrometry (qv) (fab/ms), which allows determinations of mol wt up to 2500 d with high accuracy (16, 17).

Many labeling systems have been used for dalbaheptide structures. The one used herein, where each of the seven amino acids is identified by a number (see Table 2) and each atom by a letter, is widely applied because it permits easy comparison of ^{1}H and ^{13}C nmr data (31). The IUPAC system, utilized in *Chemical Abstracts* and generally in the description of semisynthetic derivatives, requires decodification for comparison of different dalbaheptides (83).

Table 1. Naturally Occurring Dalbaheptides

Antibiotic	Producing organism	Year[a]	Company or Institute	Refs.
ristocetin A, B	*Nocardia lurida*NRRL 2430	1953	Abbott	(1, 2)
vancomycin	*Streptomyces orientalis*NRRL 2450	1955	Lilly	(1, 6, 10–13)
actinoidin A, B	*Proactinomycesactinoides*	1956	Research Institute forthe Discovery of NewAntibiotics, Moscow	(1, 18, 19)
K-288	*Streptomycesharanomachiensis*n.sp	1961	Tohoku University,Sendai	20
ristomycin A, B	*Proactinomyces fructiferi*var. *ristomycini*	1962	Research Institute forthe Discovery of NewAntibiotics, Moscow	(1, 2)
avoparcin (LL-AV290complex)	*Streptomyces candidus*NRRL 3218	1966	American Cyanamid	(21–24)
AM374	*Streptomyceseburosporeus*NRRL 3582	1969	American Cyanamid	25
A477	*Actinoplanes* sp.NRRL 3884	1971	Lilly	26
actaplanin (A4696complex)	*Actinoplanesmissouriensis*ATCC 23342	1971	Lilly	(27–29)
AB-65	*Saccharomonosporaviride* T-80	1973	DainipponPharmaceuticals	30
teicoplanin(teichomycincomplex)	*Actinoplanesteichomyceticus*ATCC 31121	1975	Lepetit	(7, 31–33)
A35512 complex	*Streptomyces candidus*NRRL 8156	1976	Lilly	(34–36)
OA-7653A, B	*Streptomyceshygroscopicus* subsp.*hiwasaensis*ATCC 31613	1978	Otsuka Pharmaceutical	(37, 38)
A51568A (*N*-demethyl-vancomycin), B	*Nocardia orientalis*NRRL 15232	1982	Lilly	(39, 40)
A41030 complex	*Streptomyces virginiae*NRRL 15156	1982	Lilly	(41–43)
A47934	*Streptomyces toyocaensis*NRRL 15009	1982	Lilly	(43–45)
ardacin (AAD-216complex, aridicin)	*Kibdelosporangiumaridum* ATCC 39323	1983	Smith, Kline andFrench	(15, 46–48)
chloropolysporin A,B, C	*Faenia interjecta* sp.nov. FERM BP-538	1983	Sankyo	(49–51)
A40926 complex	*Actinomadura*sp.ATCC 39727	1984	Lepetit	(52–54)
M43 complex	*Nocardia orientalis*NRRL 2450	1984	Lilly	55
kibdelin (AAD-609complex)	*Kibdelosporangiumaridum* subsp. *largum*ATCC 39922	1985	Smith, Kline andFrench	(56, 57)
izupeptin A, B	*Nocardia* sp.FERM P-8656	1986	Kitasato Institute,Tokyo	58
parvodicin (AAJ-271)	*Actinomadura parvosata*ATCC 53463	1986	Smith, Kline andFrench	59
synmonicin A, B, C(CWI-785)	*Synnemomycesmamnoorii*ATCC 53296	1986	Eskayef Ltd.; Smith,Kline and French	60
actinoidin A_2	*Nocardia* sp.SKF-AAJ-193	1987	Smith, Kline andFrench	(61, 62)
orienticin (PA)	*Nocardia orientalis*PA-42867	1987	Shionogi	(63, 64)
eremomycin	*Actinomyces* sp. INA-238	1987	Institute of NewAntibiotics, Academyof Medical Sciences,Moscow	(8, 65)
A42867	*Nocardia* sp. nov.ATCC 53492	1987	Lepetit	66
A82846 A, B, C	*Amycolatopsis orientalis*NRRL 18098	1987	Lilly	(67–70)
UK-68,597	*Actinoplanes* sp.ATCC 53533	1987	Pfizer	(71, 72)
helvecardin A, B	*Pseudonocardiacompacta* subsp.*helvetica* SANK 65185	1988	Sankyo	73

Table 1. ***Continued***

Antibiotic	Producing organism	Year[a]	Company or Institute	Refs.
chloroorienticins A, B,C, D, E (PA-45052)	*Amycolatopsis orientalis*PA-45052	1988	Shionogi	(69, 74, 75)
A80407 A, B	*Kibdelosporangiumphilippinensis*NRRL 18198	1989	Lilly	76
MM 45289, MM 47756	*Amycolatopsis orientalis*NCIB 12531	1989	Beecham	77
MM 47761, MM 49721	*Amycolatopsis orientalis*NCIB 12608	1989	Beecham	78
MM 47766, MM 47767,MM 55256, MM 55260	*Amycolatopsis orientalis*NCIB 40011	1989	Beecham	79
MM 49728, MM 55266,MM 55267, MM 55268	*Amycolatopsis* sp.NCIB 40089	1989	Beecham	80
decaplanin	*Actinomyces* sp.DSM 4763	1990	Hoechst	81
UK-72,051	*Amycolatopsis orientalis*n.sp.	1990	Pfizer	82

[a]Year of patent or first publication.

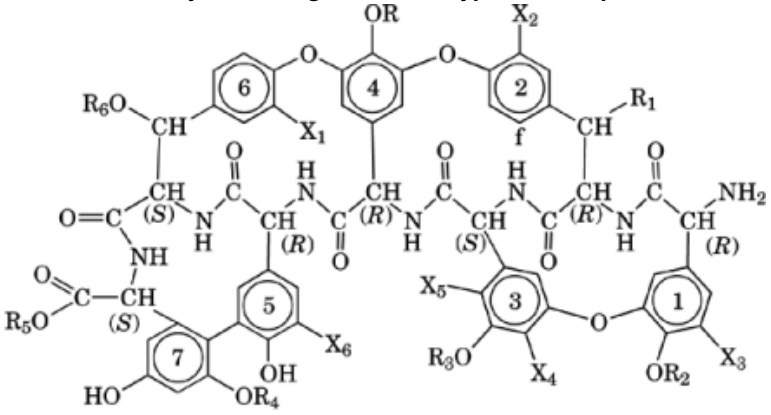
1.1. Descriptive Chemistry

Five of the seven amino acids that form the peptidic skeleton are common to all dalbaheptides: amino acid 2 is a tyrosine facultatively β-hydroxylated; amino acids 4 and 5 are *p*-hydroxyphenylglycines; 6 is a β-hydroxytyrosine and 7, the carboxy terminal, is a *m,m′*-dihydroxyphenylglycine. Oxygen bonds between the phenyl moieties of amino acids 2 and 4 and 4 and 6 form two adjacent rings. Another ring is formed by a C—C bond between the phenyl moieties of amino acids 5 and 7. The remaining two amino acids 1 and 3, help to classify all known dalbaheptides into four types. The ristocetin-type (Tables 2 and 3) where amino acid 1, the terminal NH_2, is a *p*-hydroxyphenylglycine and 3 is a *m,m′*-dihydroxyphenylglycine; an ether bond between these phenyl moieties generates an extra ring. The vancomycin-type (Table 4) where amino acids 1 and 3 are aliphatic, usually leucine and asparagine; in OA-7653A,B amino acid 1 is alanine; amino acid 3 is glutamine in OA-7653A (**40**), A51568B (**43**), glutamic acid in OA-7653B (**41**) and aspartic acid in M43B (**45**). The actinoidin-type (Table 5) where amino acid 1 is always a *p*-hydroxyphenylglycine and amino acid 3 is a phenylalanine or *p*-hydroxyphenylglycine. Only a few dalbaheptides belong to this group. And synmonicin (Table 6) which is the only example of a dalbaheptide where amino acid 1 is aromatic (*p*-hydroxyglycine) and amino acid 3 is a thioamino acid such as methionine.

Dalbaheptides of natural origin have small variations in the nature and position of substituents. Additional chemical features are (*1*) chlorine atoms (up to four), methyl, and additional hydroxyl groups that can be present in different positions in the phenyl residues. No chlorine is present in ristocetins (**1**), (**2**), orienticin C (**50**), or MM 49721 (**60**). (*2*) Simple or complex carbohydrates that are linked to the core peptide in one or more positions through hemiacetalic bonds. Sugars found in dalbaheptides can be neutral, basic, or acidic. Vancosamine, *epi*-vancosamine, ristosamine, actinosamine, and acosamine were first isolated from dalbaheptides. A41030A (**11**), B (**12**), E (**14**), and A47934 (**16**) do not carry any sugar; minor amounts of partially (pseudoaglycones) or totally (aglycones) deglycosylated dalbaheptides are often present in many normally recovered batches. These compounds can be natural metabolites or artifacts of the recovery and purification processes. (*3*) A phenolic hydroxyl is esterified as a sulfate monoester in A47934 (**16**) and UK-68,597 (**17**). (*4*) The terminal carboxyl in ristocetin and actaplanin is a methyl ester and the terminal amino group can be methylated. In UK-68,597 (**17**) the *N*-terminal residue is replaced by a ketoamide functionality. (*5*) The amino group of glucosamine or 2-amino-2-deoxyglucuronic acid linked to the *p*-hydroxyphenyl residue of amino acid 4 of some ristocetin-type dalbaheptides is acylated by 10–12 carbon fatty acid residues. The acyl chains may be linear or branched (iso or anteiso), only exceptionally unsaturated. Acyl derivatives are present in teicoplanins,

ardacins, A40926, kibdelins, and parvodicins and are therefore subgrouped as lipodalbaheptides (Table 3). The side chains differentiate the components of each complex.

Table 2. Naturally Occurring Ristocetin-type Dalbaheptides



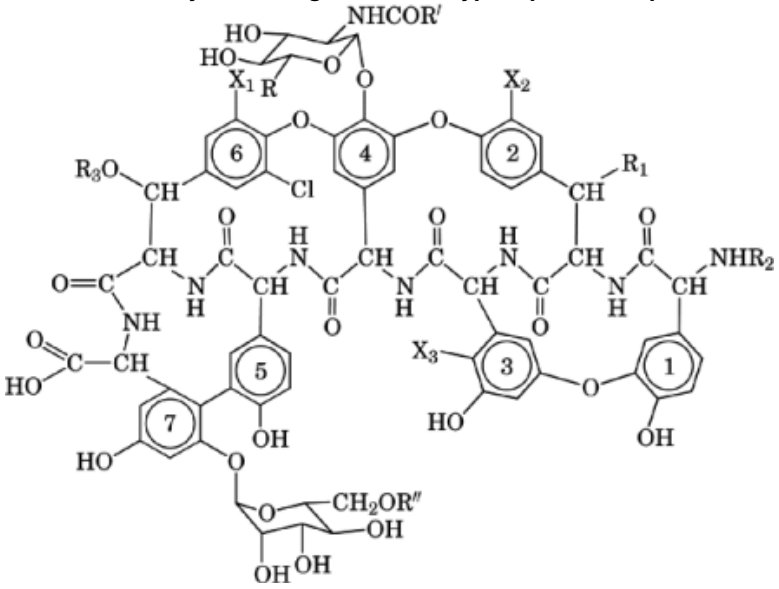
Antibiotic	CAS Registry Number	Structure[a] No.	R	R_1	R_2	R_3	R_4	R_5	R_6	X_1	X_2	X_3	X_4	X_5	X_6
ristocetin															
A[b]	[11021-66-2]	(**1**)	L–rha ⟶ D–glu ⟵ D–man ⟵ D–ara	OH	H	H	D-man	CH_3	L-ria	H	H	H	CH_3	H	H
B[c]	[1405-59-01]	(**2**)	L–rha ⟶ D–glu	OH	H	H	D-man	CH_3	L-ria	H	H	H	CH_3	H	H
actaplanin															
A	[88357-81-7]	(**3**)	D–glu ⟵ man	H	H	D-man	D-man	CH_3	L-ria	Cl	H	H	CH_3	H	H
B_1	[88357-82-8]	(**4**)	D–glu ⟵ rha	H	H	D-man	D-man	CH_3	L-ria	Cl	H	H	CH_3	H	H
B_2	[88357-83-9]	(**5**)	D-glu	H	H	D-man	D-man	CH_3	L-ria	Cl	H	H	CH_3	H	H
B_3	[88357-84-0]	(**6**)	D–glu ⟵ man	H	H	H	D-man	CH_3	L-ria	Cl	H	H	CH_3	H	H
C_1	[88357-85-1]	(**7**)	D–glu ⟵ L–rha	H	H	H	D-man	CH_3	L-ria	Cl	H	H	CH_3	H	H
C_3	[88357-88-4]	(**8**)	D-glu	H	H	D-man	H	CH_3	L-ria	Cl	H	H	CH_3	H	H
G	[88381-73-1]	(**9**)	D-glu	H	H	H	man	CH_3	L-ria	Cl	H	H	CH_3	H	H
A35523 B	[63849-30-9]	(**10**)	glu ⟵ rha	OH	H	fuc	man	CH_3	3-*epi*-L-van	H	H	H	H	Cl	H
A41030															
A	[89139-41-3]	(**11**)	H	H	H	H	H	H	H	Cl	Cl	H	H	H	Cl
B	[89139-42-4]	(**12**)	H	H	H	H	H	H	H	Cl	Cl	H	H	H	H
C	[89140-21-6]	(**13**)	H	H	gal	H	H	H	H	Cl	Cl	H	H	H	Cl
E	[89139-43-5]	(**14**)	H	H	H	H	H	H	H	Cl	H	H	H	H	H
F	[89140-20-5]	(**15**)	H	H	gal ⟶ gal	H	H	H	H	Cl	Cl	H	H	H	Cl
A47934	[90039-80-8]	(**16**)	H	H	SO_3H	H	H	H	H	Cl	Cl	H	H	H	Cl
UK-68,597[d]	[121377-12-6]	(**17**)	glu ⟵ van	H	H	SO_3H	H	H	H	Cl	Cl	Cl	H	H	Cl

[a]Abbreviations are ria = ristosamine, van = vancosamine, man = mannose, rha = rhamnose, glu = glucose, gal = galactose, ara = arabinose, and fuc = fucose.
[b]Identical to ristomycin A.
[c]Identical to ristomycin B.
[d]A C═O group is present instead of the terminal CH—NH_2.

1.2. Producing Organisms

All the dalbaheptides so far described are produced by strains belonging to the order of *Actinomycetales* (Table 1). Additionally, co-fermentation of *Actinoplanes missiouriensis* NRRL 15647 and strain NRRL 15646, which was obtained by chemical mutagenesis of an actaplanin-producing strain, yielded antibiotic CUC/CSV, an actaplaninlike dalbaheptide having a C═O function instead of the terminal HC–NH (84). An *Actinoplanes teichomyceticus* mutant yielded high levels of two teicoplaninlike compounds, designated RS-3 and RS-4, carrying 6-methyloctanoic and *n*-nonanoic vesiolues as fatty acid chains (85, 86).

Table 3. Naturally Occurring Ristocetin-type Lipodalbaheptides



Antibiotic	CAS Registry Number	Structure[a] No.	R	R′	R″	R_1	R_2	R_3	X_1	X_2	X_3
teicoplanin											
T-A2-1	[91032-34-7]	(**18**)	CH_2OH	$(CH_2)_2CH{=}CH(CH_2)_4CH_3$	H	H	H	Ac-*N*-D-glu	H	Cl	H
T-A2-2	[91032-26-7]	(**19**)	CH_2OH	$(CH_2)_6CH(CH_3)_2$	H	H	H	Ac-*N*-D-glu	H	Cl	H
T-A2-3	[91032-36-9]	(**20**)	CH_2OH	$(CH_2)_8CH_3$	H	H	H	Ac-*N*-D-glu	H	Cl	H
T-A2-4	[91032-37-0]	(**21**)	CH_2OH	$(CH_2)_6CH(CH_3)CH_2CH_3$	H	H	H	Ac-*N*-D-glu	H	Cl	H
T-A2-5	[91032-38-1]	(**22**)	CH_2OH	$(CH_2)_7CH(CH_3)_2$	H	H	H	Ac-*N*-D-glu	H	Cl	H
ardacin											
A	[95935-21-0]	(**23**)	COOH	$(CH_2)_8CH_3$	H	OH	CH_3	H	Cl	Cl	Cl
B	[95935-22-1]	(**24**)	COOH	$(CH_2)_7CH(CH_3)_2$	H	OH	CH_3	H	Cl	Cl	Cl
C	[95935-23-2]	(**25**)	COOH	$(CH_2)_8CH(CH_3)_2$	H	OH	CH_3	H	Cl	Cl	Cl
A40926											
A[b]	[102961-73-9]	(**26**)	COOH	$(CH_2)_9CH_3$	H	H	CH_3	H	H	H	Cl
B[c]	[102961-74-0]	(**27**	COOH	$(CH_2)_8CH(CH_3)_2$	H	H	CH_3	H	H	H	Cl

Table 3. ***Continued***

Antibiotic	CAS Registry Number	Structure[a] No.	R	R′	R″	R_1	R_2	R_3	X_1	X_2	X_3
PA	[102961-76-2]	(**28**)	COOH	$(CH_2)_9CH_3$	$COCH_3$	H	CH_3	H	H	H	Cl
PB[d]	[102961-77-3]	(**29**)	COOH	$(CH_2)_8CH(CH_3)_2$	$COCH_3$	H	CH_3	H	H	H	Cl
kibdelin											
A	[103528-50-3]	(**30**)	CH_2OH	$(CH_2)_8CH_3$	H	OH	CH_3	H	Cl	Cl	Cl
B	[103528-49-0]	(**31**)	CH_2OH	$(CH_2)_7CH(CH_3)_2$	H	OH	CH_3	H	Cl	Cl	Cl
C_1	[103549-47-9]	(**32**)	CH_2OH	$(CH_2)_8CH(CH_3)_2$	H	OH	CH_3	H	Cl	Cl	Cl
C_2	[105997-85-1]	(**33**)	CH_2OH	$(CH_2)_{10}CH_3$	H	OH	CH_3	H	Cl	Cl	Cl
D	[105997-86-2]	(**34**)	CH_2OH	$(CH_2)_2CH{=}CH(CH_2)_4CH_3$	H	OH	CH_3	H	Cl	Cl	Cl
parvodicin											
A	[114797-09-9]	(**35**)	COOH	$(CH_2)_8CH_3$	H	H	CH_3	H	H	H	Cl
B_1	[110882-82-1]	(**36**)	COOH	$(CH_2)_7CH(CH_3)_2$	H	H	CH_3	H	H	H	Cl
C_2	[110882-85-4]	(**37**)	COOH	$(CH_2)_{10}CH_3$	H	H	CH_3	H	H	H	Cl
C_4	[110882-87-6]	(**38**)	COOH	$(CH_2)_{10}CH_3$	$COCH_3$	H	CH_3	H	H	H	Cl

[a] Ac−*N*−D−glu = *N*−acetyl−D−glucosamine.
[b] Identical to parvodicin B_2.
[c] Identical to parvodicin C_1.
[d] Identical to parvodicin C_3.

1.3. Screening

The dalbaheptides were at first isolated by conventional screening procedures. More recently mechanistically based screens have been devised. For example, bioselective adsorption on affinity resins made by immobilizing *N*-acetyl-D-Ala-D-Ala [19993-26-1] on an activated support (87, 88) was used in a screening campaign in which 72 strains were identified as producers of dalbaheptides, 60% of which produced ristocetin (89). The other characterized dalbaheptides were teicoplanins (Table 3), avoparcins (Table 5), actaplanins (Table 2), and the novel molecules A40926 (Table 3) and A42867 (**53**).

Other specific discovery assays have been used such as differential inhibition of a vancomycin resistant *S. aureus* strain and its susceptible parent, and an assay based on antagonism of the antibacterial activity by *N,N*-diacetyl-L-Lys-D-Ala-D-Ala [24570-39-6], a tripeptide analogue of the dalbaheptides receptor. Application of this latter test to 1936 cultures (90) led to the isolation of 42 dalbaheptides, six of which, including kibdelin (Table 3), parvodicin (Table 3), and actinoidin A_2 (**68**) were novel. A colorimetric assay based on competition between horseradish peroxidase bound teicoplanin and the putative dalbaheptide for a D-Ala-D-Ala peptide attached to the test tube wall has also been utilized (89, 91) as has a polyclonal antibody against vancomycin, an enzyme-linked immunosorbant analysis (ELISA), which led to the discovery of A82846 (68).

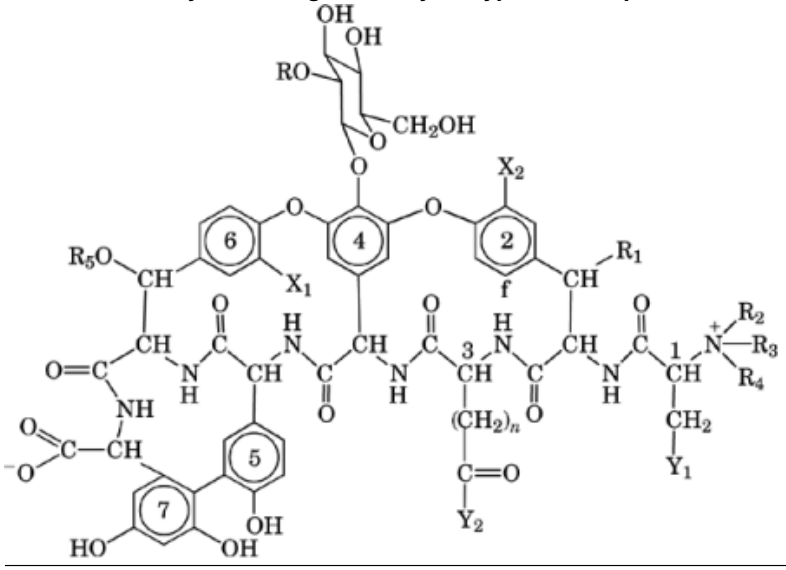
1.4. Fermentation

Dalbaheptides are produced by submerged fermentation (qv) and this topic has been reviewed (92). In a few cases addition of a biosynthetic precursor of the core aglycones such as tyrosine and *p*-hydroxyphenylglycine, increased the yields (39). It has been reported (93) that the fatty acid moieties of teicoplanin (Table 3) biosynthetically derive from the degradation of long-chain fatty acids present in the membranes of the producing microorganisms. Addition to fermentation media of precursors that alter the membrane fatty acid composition led to an altered ratio of the components of teicoplanin (94, 95) and A40926 (96).

1.5. Recovery and Purification

The dalbaheptides are present in both the fermentation broth and the mycelial mass, from which they can be extracted with acetone or methanol, or by raising the pH of the harvested material, eg, to a pH of 10.5–11 for A47934 (**16**) (44) and A41030 (41) and actaplanin (Table 2) (28). A detailed review on the isolation of dalbaheptides has been written (14). Recovery from aqueous solution is made by ion pair (avoparcin) or butanol (teicoplanin) extraction. The described isolation schemes use ion-exchange matrices such as Dowex and Amberlite IR, acidic alumina, cross-linked polymeric adsorbents such as Diaion HP and Amberlite XAD, cation-exchange dextran gel (Sephadex), and polyamides in various sequences. Reverse-phase hplc, ion-exchange, or affinity resins may be used for further purification (14, 89).

Table 4. Naturally Occurring Vancomycin-type Dalbaheptides



Antibiotic	CAS Registry Number	Structure[a] No.	n	R	R_1	R_2	R_3	R_4	R_5	X_1	X_2	Y_1	Y_2
vancomycin[b]	[1404-90-6]	(**39**)	1	L-van	OH	H	H	CH_3	H	Cl	Cl	iC_3H_7	NH_2
OA-7653													
A	[73699-70-4]	(**40**)	2	[c]	H	H	CH_3	CH_3	D-glu	Cl	Cl	H	NH_2
B	[112219-76-8]	(**41**)	2	[c]	H	H	CH_3	CH_3	D-glu	Cl	Cl	H	OH
A51568													
A	[92182-33-7]	(**42**)	1	L-van	OH	H	H	H	H	Cl	Cl	iC_3H_7	NH_2
B	[92182-32-6]	(**43**)	2	L-van	OH	H	H	H	H	Cl	Cl	iC_3H_7	NH_2
M43													
A	[99759-15-6]	(**44**)	1	L-van	OH	CH_3	CH_3	CH_3	H	Cl	Cl	iC_3H_7	NH_2
B	[99776-55-3]	(**45**)	1	L-van	OH	CH_3	CH_3	CH_3	H	Cl	Cl	iC_3H_7	OH
C	[99759-14-5]	(**46**)	1	H	OH	CH_3	CH_3	CH_3	H	Cl	Cl	iC_3H_7	NH_2
D	[99759-13-4]	(**47**)	1	L-van	OH	H	CH_3	CH_3	H	Cl	Cl	iC_3H_7	NH_2
orienticin													
A[d]	[111073-20-2]	(**48**)	1	4-*epi*-van	OH	H	H	CH_3	4-*epi*-van	Cl	H	iC_3H_7	NH_2
B	[111073-19-9]	(**49**)	1	L-oli	OH	H	H	CH_3	4-*epi*-van	Cl	H	iC_3H_7	NH_2
C[e]	[112848-47-2]	(**50**)	1	4-*epi*-van	OH	H	H	CH_3	4-*epi*-van	H	H	iC_3H_7	NH_2
D	[112848-46-1]	(**51**)	1	4-*epi*-van	OH	H	CH_3	CH_3	4-*epi*-van	Cl	H	iC_3H_7	NH_2
eremomycin[f]	[110865-90-2]	(**52**)	1	4-*epi*-van	OH	H	H	CH_3	4-*epi*-van	H	Cl	iC_3H_7	NH_2
A42867	[114540-35-1]	(**53**)	1	D-rha	OH	H	H	CH_3	van	H	Cl	iC_3H_7	NH_2

Table 4. ***Continued***

Antibiotic	CAS Registry Number	Structure[a] No.	n	R	R_1	R_2	R_3	R_4	R_5	X_1	X_2	Y_1	Y_2
chloroorienticin													
A[g]	[118395-73-6]	(**54**)	1	4-*epi*-van	OH	H	H	CH_3	4-*epi*-van	Cl	Cl	iC_3H_7	NH_2
B	[118373-81-2]	(**55**)	1	H	OH	H	H	CH_3	4-*epi*-van	Cl	Cl	iC_3H_7	NH_2
C	[118373-82-3]	(**56**)	1	[c]	OH	H	CH_3	CH_3	4-*epi*-van	Cl	Cl	iC_3H_7	NH_2
D	[118373-83-4]	(**57**)	1	4-*epi*-van	OH	H	CH_3	CH_3	4-*epi*-van	Cl	Cl	iC_3H_7	NH_2
E	[118373-84-5]	(**58**)	1	H	OH	H	CH_3	CH_3	4-*epi*-van	Cl	Cl	iC_3H_7	NH_2
MM 47761[h]	[126985-51-1]	(**59**)	1	rha	OH	H	H	CH_3	4-*epi*-van	H	Cl	iC_3H_7	NH_2
MM 49721	[126985-52-2]	(**60**)	1	rha	OH	H	H	CH_3	4-*epi*-van	H	H	iC_3H_7	NH_2

[a] Abbreviations are van = vancosamine, glu = glucose, oli = olivose, $4-epi-$van = $4-epi-$vancosamine = eremosamine.
[b] Identical to K-288.
[c] The hydroxyl on ring 4 does not carry any sugar.
[d] Identical to UK-72,051.
[e] Identical to A82846C, MM 47756.
[f] Identical to A82846A, MM 45289.
[g] Identical to A82846B.
[h] Identical to decaplanin.

1.6. Physical Properties

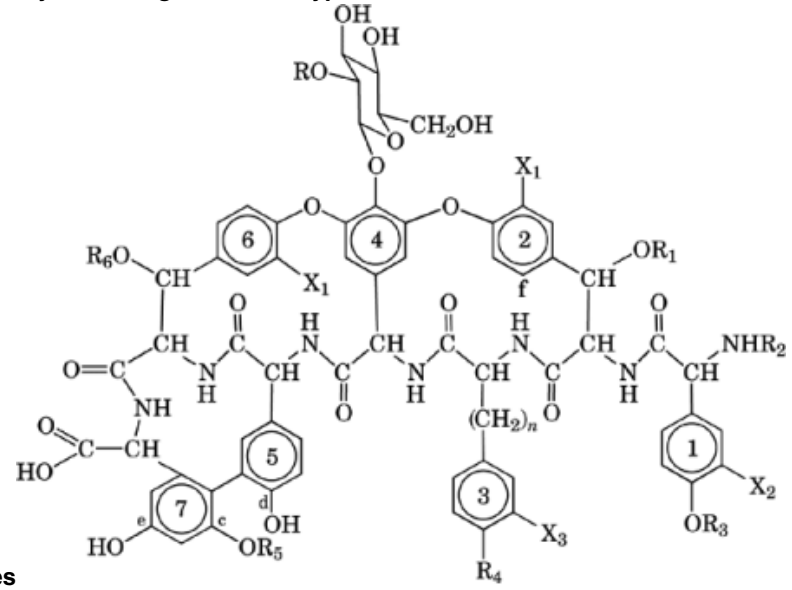
The molecular weight of dalbaheptides ranges from about 1150 to 2200. Pure dalbaheptides are obtained as colorless or whitish amorphous powders that usually retain water and solvent. Dalbaheptides are generally water-soluble. Teicoplanin can be obtained as an internal salt or as a partial monoalkaline (sodium) salt depending on the pH of the aqueous solution in the final purification step. Other dalbaheptides are obtained as acidic salts, such as hydrochlorides (vancomycin, actaplanin) or sulfates (ristocetin A, avoparcin, eremomycin). The presence of amino, carboxyl, benzylic, and phenolic hydroxyl functions, sugars, and aliphatic chains influence both water solubility and total charge. Aqueous solutions of vancomycin (**39**) at pH 3–5 and of teicoplanins (Table 3) at pH 7.4 are stable. The isoelectric points (pI) of dalbaheptides, determined by electrofocusing, vary from 3.2 for A47934 (**16**) to 8.1 for ristocetin (Table 2), A477, and A42867 (**53**). The lipid–water partition coefficient in *n*-octanol buffer is -1.1 at pH 5.1 for teicoplanin (Table 3) and -2.5 for vancomycin (39) indicating that teicoplanin is 5–10 times less hydrophilic than vancomycin.

Dalbaheptides are levorotatory. The absolute configuration of vancomycin was determined by x-ray analysis of degradation product CDP-I [79517-31-0] (11). The configurations of the seven amino acids are 1(*R*), 2(*R*), 3(*S*), 4(*R*), 5(*R*), 6(*S*), and 7(*S*) (Table 2). Nmr experiments provided evidence that the stereochemistry of the chiral centers and the overall three-dimensional conformation is the same for most dalbaheptides. Natural and chemically produced epimers are exceptions. The anomeric conformation and position of the sugars have also been determined by nmr. In teicoplanin five of the conformations of the amide linkages are trans, the **5–6** linkage is cis. The stereostructure of teicoplanin aglycone is shown in Figure 1.

1.7. Biosynthesis

Biochemical studies on dalbaheptides have been reviewed (92, 97). Experiments with ^{13}C and ^{2}H have shown that in vancomycin (**39**), D-tyrosine is the precursor of D-*p*-hydroxyphenylglycine and β-hydroxy-*m*-chlorotyrosine, and acetate the precursor of the two *m,m′*-dihydroxyphenylglycines (98). Similar results using either ^{13}C or radioactively labeled material have been reported for avoparcin (Table 5) (23), ristocetin (Table 2) (99, 100), ardacin (Table 3) (101), and A47934 (102).

Table 5. Naturally Occurring Actinoidin-type Dalbaheptides



Antibiotic	CAS Registry Number	Structure[a] No.	n	R	R_1	R_2	R_3	R_4	R_5	R_6	X_1	X_2	X_3
actinoidin													
A	[60382-78-7]	(**61**)	1	L-aco	H	H	H	H	D-man	L-aca	H	H	H
B	[60382-79-8]	(**62**)	1	L-aco	H	H	H	H	D-man	L-aca	H	Cl	H
chloropolysporin													
α	[73957-86-5]	(**63**)	0	L-ria	D-man	CH_3	L-rha	OH	H	L-ria	H	H	H
β	[73957-87-6]	(**64**)	0	L-ria	D-man	CH_3	L-rha	OH	H	L-ria	H	H	Cl
ϵ	[88899-52-9]	(**65**)	0	L-ria	H	CH_3	L-rha	OH	H	L-ria	H	H	Cl
chloropolysporin													
B	[105650-11-1]	(**66**)	0	H	man	CH_3	rha	OH	H	ria	Cl	H	Cl
C	[105650-12-2]	(**67**)	0	H	man	CH_3	H	OH	H	ria	Cl	H	Cl
actinoidin A_2	[108905-13-1]	(**68**)	1	L-rha	H	H	H	H	D-man	L-aca	H	H	H
helvecardin													
A	[119979-33-8]	(**69**)	0	ria	man	CH_3	*O*-Me-rha	OH	H	ria	H	H	Cl
B	[119979-34-9]	(**70**)	0	ria	H	CH_3	*O*-Me-rha	OH	H	ria	H	H	Cl
MM 47767[b]	[129772-77-6]	(**71**)	1	aco	H	CH_3	H	H	H	aca	H	Cl	H
MM 55256[b]	[129652-26-2]	(**72**)	1	aco	H	CH_3	H	H	H	aca	H	Cl	H

[a]Abbreviations are aco = acosamine, aca = actinosamine, ria = ristosamine, man = manhose, rha = rhamnose, and $O-\mathrm{Me}-\mathrm{rha}$ = 2-*O*-methylrhamnose.

[b]These two dalbaheptides differ with regard to the steric position of the terminal NCH_3 group. One *O*-mannosyl group is present in position 5d, 7c, or 7e.

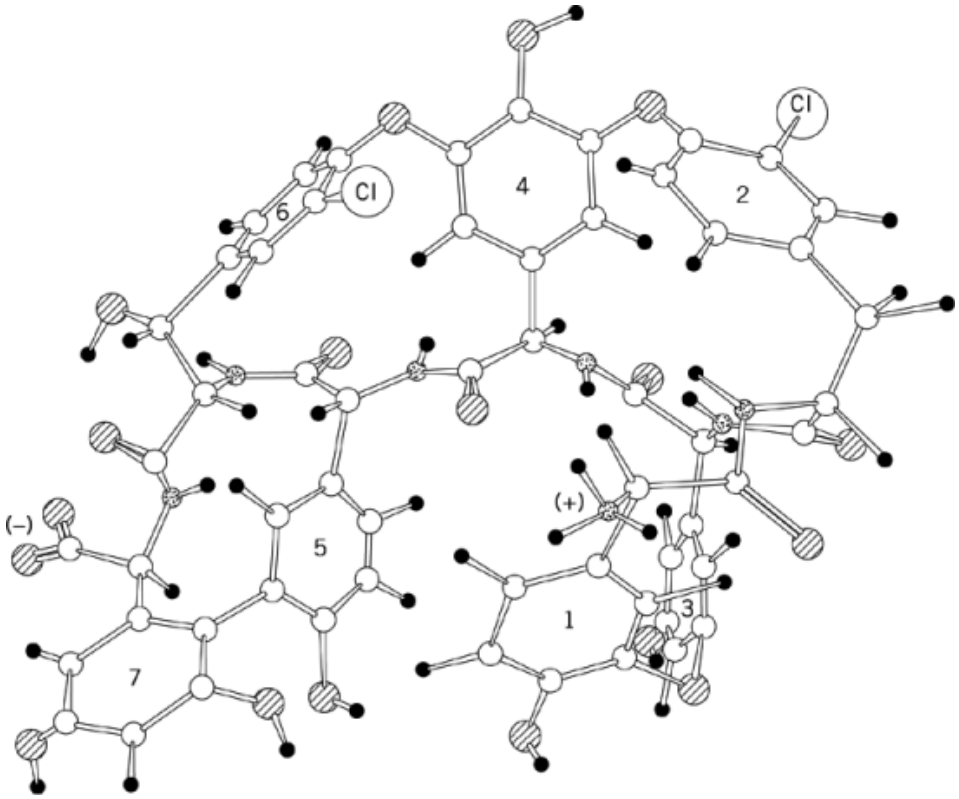


Fig. 1. Stereostructure of teicoplanin aglycone [89139-42-4] obtained from a Dreiding model (83) where • is hydrogen, ◍ is nitrogen, ○ is carbon, ◍ is oxygen. The numbers represent the seven amino acids.

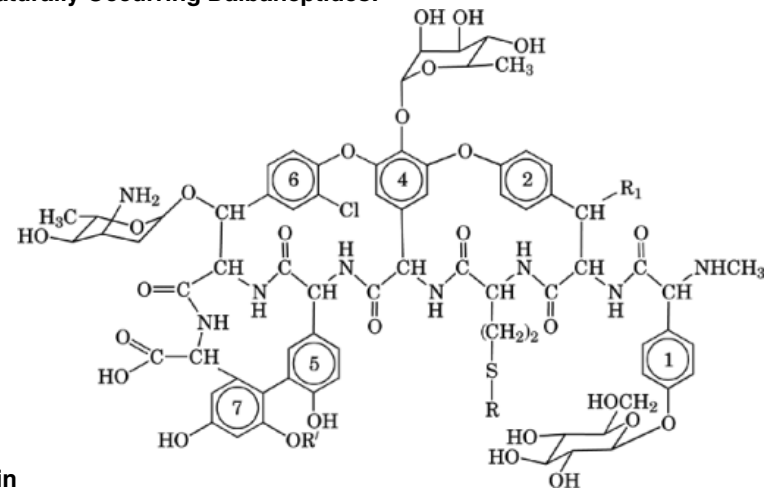
Kibdelins (Table 3) are converted into the corresponding ardacins by cultures of *Kibdelosporangium aridum* indicating that the oxidation of carbon-6 of glucosamine to a carboxy group is the last biosynthetic step (100). Addition of ^{14}C-labeled ardacin aglycone to cultures of *K. aridum* gave origin to labeled ardacins but the yields were so low it is doubtful that the aglycone is the precursor of the glycosylated product. Other studies showed that the sulfate ester on phenolic hydroxyl in the production of A47934 (**16**) occurs prior to the formation of microbiologically active intermediates (102).

2. Biological Properties

2.1. Mechanism of Action

The basis of the antibacterial action of dalbaheptides is the ability to form a complex with the terminal D-Ala-D-Ala residues of growing peptidoglycan chains, thus preventing transglycosylation, eg, chain elongation, and transpeptidation, eg, cross-linking. The consequent defective cell wall stops bacterial growth and eventually leads to cell death. The mechanism of action has been reviewed both at the molecular (3) and at the biochemical level (4). Addition of a dalbaheptide to a growing culture results in rapid inhibition of incorporation of acetylglucosamine, a specific precursor of cell wall synthesis, and in accumulation of UDP-*N*-acetylmuramyl pentapeptide. Direct interaction studies of dalbaheptides and D-Ala-D-Ala-containing synthetic peptides have

Table 6. Naturally Occurring Dalbaheptides:



Synmonicin

Synmonicin	CAS Registry Number	Structure[a] No.	R	R′	Empiricalformula
A	[114836-24-7]	(**73**)	(O)CH_3	man	$C_{80}H_{86}ClN_8O_{34}$
B[b]	[114836-22-5]	(**74**)	CH_3	man	$C_{80}H_{86}ClN_8O_{33}$
C	[114836-68-3]	(**75**)	CH_3	H	$C_{74}H_{76}ClN_8O_{28}S$

[a]Abbreviation is man = mannose.
[b]Mixture of two epimers at terminal HC–NH, B′ is (*R*); B″ is (*S*).

been carried out. Binding of dalbaheptides to D-Ala-D-Ala models has been measured by uv differential spectroscopy (3), affinity chromatography (87), microcalorimetry (103), nmr spectrometry (104), displacement of polyacrylamide-bound vancomycin (**39**) (105), and displacement of radiolabeled ristocetin bound to bacterial cells (106). These studies indicate that a free carboxyl and a D-configuration of the terminal amino acid of the model peptide are absolute requirements for formation of the complex. Stereostructure of the dalbaheptide skeleton forms a sort of receptor pocket which accommodates the D-Ala-D-Ala terminus of the target (3, 107).

2.2. Antibacterial Activity

2.2.1. In Vitro Properties

The antibacterial spectrum of most dalbaheptides is known (Table 1). Vancomycin (**39**) and/or teicoplanin (Table 3) are generally introduced as reference compounds. Direct comparative data for some dalbaheptides tested under the same experimental conditions are given in Table 7 (54).

Dalbaheptides are active almost exclusively against gram-positive microorganisms including all major pathogens such as *staphylococci*, coagulase-positive and negative, *streptococci* of all groups, *enterococci* including *E. faecalis* and *faecium*, *corynebacteria* including JK and *acnes*, *Clostridia* including *C. perfringens* and *C. difficile*, anaerobic cocci eg, *peptococci* and *streptostreptococci*, and *Listeria monocytogenes*. Gram-positive organisms naturally resistant to dalbaheptides include *Lactobacilli*, *Leuconostoc*, *Pediococcus*, and *Nocardia*. Lipodalbaheptides are in general less active than other dalbaheptides against CNS. For example, the MIC against *S. haemolyticus* is from 4 to 50 μg/mL.

Table 7. Antibacterial Activity of Dalbaheptides, MICs in μg/mL[a]

	Organism and strain					
Antibiotic	*Staphylococcus aureus* TOUR	*Staphylococcus epidermidis* ATCC 12228	*Streptococcus pyogenes* C 203	*Enterococcus faecalis* ATCC 7080	*Clostridium perfringens* ISS 30543	*Neisseria gonorroheae* ISM 68/126
ristocetin[b]	4	2	0.25	1	2	64
vancomycin[c]	0.25	0.5	0.13	0.5	0.13	32
avoparcin[d]	2	2	0.25	0.25	0.5	128
actaplanin[b]	1	2	0.13	0.5	1	>128
teicoplanin[e]	0.13	0.13	0.06	0.13	0.03	32
A35512B[d]	1	0.5	0.13	0.5	2	64
A41030[b]	0.03	0.008	0.13	0.13		64
A47934[b]	0.06	0.03	0.13	0.13	0.25	8
ardacin[e]	1	4	0.13	2	0.06	64
A40926[e]	0.06	0.06	0.06	0.06	0.004	2

[a] From Ref. 54 and the Author's Laboratory.
[b] Structures shown in Table 2.
[c] Structure (**39**).
[d] Structures shown in Table 5.
[e] Structures shown in Table 3.

Gram-negative organisms are unsusceptible except *Gardnerella vaginalis* and *Branhamella catarrhalis* which are susceptible to teicoplanin, and *Neisseria gonorrhoeae* (Table 7). However, A47934 and A40926 (54) are exceptionally active against *N. gonorrhoeae*, having MICs of 8 and 2 μg/mL, respectively.

In the parvodicin and teicoplanin series (Table 3) the nature and length of the fatty acid portion of the glycolipid moiety only slightly influence the activity *in vitro*. Dalbaheptides are bactericidal against actively growing, but not against resting, bacteria (33).

2.2.2. In Vivo Properties

The efficacy of dalbaheptides has been assessed in various models of experimental *septicemia* in mice. In general there was good correlation between the ED_{50}s (effective doses which prevent death in 50% of test animals) and the MICs on test strains. Teicoplanin was very effective, ED_{50} values ranged from 0.11 to 0.72 mg/kg sc administration for septicemias caused by *S. pyogenes*, *S. pneumoniae*, and *S. aureu*, whereas for vancomycin ED_{50}s were from 0.58 to 7.2 mg/kg (33). Eremomycin (**52**) had therapeutic activity 2–3 times greater than vancomycin. Therapeutic indices for staphylococcal–streptococcal sepsis exceeded ten times those of vancomycin (8). Ardacin and kibdelin are less active *in vivo* than vancomycin, although the MIC on the tested strains are comparable. This happens also for A40926 in respect to teicoplanin (54). In fact, the long lasting ardacin was more active than vancomycin when administered as early as 18 h before infection (48). Teicoplanin and vancomycin were also found to be active against experimentally induced endocarditis in rabbits (108) and rats (109), and against localized infection in mice (109).

2.3. Pharmacokinetics

Pharmacokinetic studies in mice via iv administration have been done mainly on vancomycin (**39**), eremomycin (**52**), and lipodalbaheptides (Table 3). A systematic investigation of the relationship between pI, lipophilicity, and pharmacokinetic parameters of ardacin and its hydrolysis products in comparison to those of ristocetin (Table 2), teicoplanin, and vancomycin has been carried out (110). Ardacin and its pseudoaglycone having pIs ≈ 3.8 yielded high and prolonged serum concentrations and the half-life ranged from 226 to 492 min. In contrast, vancomycin and ristocetin, which have pIs ≈ 8, had $t_{1/2} = 20$ and 62 min, respectively; teicoplanin and ardacin

aglycone, pIs ≈ 5, had intermediate elimination rates, $t_{1/2}$ ranged from 118 to 155 min. For dalhabeptides having similar pIs, clearance decreased and half-life increased as lipophilicity increased.

2.4. Mechanism of Resistance

Recently, resistance to high levels of dalbaheptides has been described in both *E. faecium* and *E. faecalis* (111). This resistance, inducible by low concentrations of dalbaheptides, is plasmid mediated and is transferable. Concomitant with the induction of resistance is the appearance or increased expression of a protein having a molecular weight of either 39,500 or 39,000. The enzymatic activity of this material has been postulated (112). Although the mechanism of resistance induction by dalbaheptides is unknown, different dalhabaheptides have different induction capacity. Vancomycin (**39**) is the most powerful inducer; teicoplanin is a very weak inducer.

3. Chemical Modifications

Although it has been known for some time that hydrolysis of ristocetin leads to derivatives having different or increased antimicrobial activity (113), little chemical modification work was reported in the literature until the mid-1980s. Selective removal of sugar moieties and glycosylation, deacylation, deamination, dechlorination, introduction of bromine or chlorine atoms, esterification or amidation of the terminal carboxyl, acylation or alkylation of the terminal (or sugar) amino groups have all since been described, mainly in patent applications. Some of the aglycones and pseudoaglycones showed a weak activity against selected gram-negative bacteria (83, 114, 115). Among the most interesting compounds produced was SKF 104662 [121089-14-3], obtained from the B′ epimer of synmonicin (Table 6) after selective removal of the neutral sugars and glycosylation of the hydroxyl on ring 4 (116). The *in vitro* activity (117) and therapeutic efficacy in experimental infection in mice for *SKF 104662* were similar to vancomycins or teicoplanins. SKF 104662 was less toxic than vancomycin in mice and the pharmacokinetic profile in mice, rats, and dogs indicated that the half-life was also longer than that of vancomycin (118).

The -$NH(CH_2)_3N(CH_3)_2$ amide of teicoplanin factor A2-2, coded MDL 62,873 [122173-74-4], was also prepared. The combined effect of a moderate basicity and a slightly increased lipophilicity at neutral pH probably led to a better penetration through the cell wall. MDL 62,873 was consistently more active than teicoplanin against CNS clinical isolates (119, 120). No semisynthetic dalbaheptide is under clinical evaluation at this writing.

4. Economic Aspects

Only three dalbaheptides are commercialized: vancomycin (**39**) and teicoplanin (**18–22**) for human health, and avoparcin (**63–65**) for animal usage. Vancomycin, the main trademark of which is Eli Lilly's Vancocin had 1990 sales around $160 million. Total annual production is in the vicinity of 8 t. Teicoplanin, trademarked Targocid, had 1990 sales of $35 million corresponding to 200 kg. Teicoplanin is commercialized in Europe, Hong Kong, Korea, and the Middle East. It is at the late developmental clinical phase in North America and Japan. Avoparcin is used as a growth promoting feed additive (see Feeds and feed additives; Growth regulators).

4.1. Clinical Use

Vancomycin and teicoplanin as formulated drugs are lyophilized powders to be reconstituted with sterile water for injection. Vancomycin hydrochloride [1404-93-9], is presented in vials of 500 mg that give 100–200 mL solution of pH 2.5–4.2. It is administered by slow (60 min) infusion at a dose of 500 mg every 6 h or 1 g every

12 h/d. The teicoplanin contains the five factors (87%) plus 13% of the pseudoaglycone T-A3-1. It is presented in vials containing 200 mg of lyophilized power that after dissolution with 3 mL of solvent gives a solution at pH 7.5. The dose regimen is 200–800 mg/d by iv bolus administration.

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