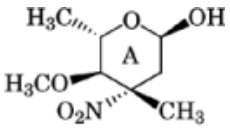
Kirk-Othmer Encyclopedia of Chemical Technology.

OLIGOSACCHARIDES

Oligosaccharide antibiotics represented by the everninomicins **(1)** (Table 1) (1–13), flambamycins **(2)** (Table 2) (22, 23), avilamycins **(2)** (Table 2) (14, 15), and curamycins **(2)** (Table 2) (18, 19) have complex and unique structural features. They are sometimes referred to as orthosomycins because characteristically these oligosaccharides possess two acid sensitive ortho-ester linkages, cleavage of which results in the complete loss of antibiotic activity (3, 22). Another structural feature common to all the oligosaccharide antibiotics is the presence of a substituted phenol ester derived from dichloroisoeverninic acid attached to the sugar ring B at C-13. This acidic phenolic group, which could form salts with organic or inorganic bases, eg, the sodium or *N*-methylglucamine salt, is also essential for the antibiotic activity (3).

An additional structural feature found in everninomicin D is the presence of a nitro sugar residue, evernitrose **(3)** linked to ring B at C-12. Everninomicins B (1), C (2), and 13-384 Component 1 (13) also have this unique nitro sugar. Chemical modification of the nitro group has led to the preparation of a number of highly active derivatives (6, 7).



(3)

The first member of the oligosaccharide antibiotics to have its complete chemical structure elucidated was everninomicin D (5). The structure of everninomicin D then represented a template for the assignment of the structures of flambamycin (23), avilamycins (14), curamycins (19), and, more recently, everninomicin 13-384 Components 1 and 5 (13).

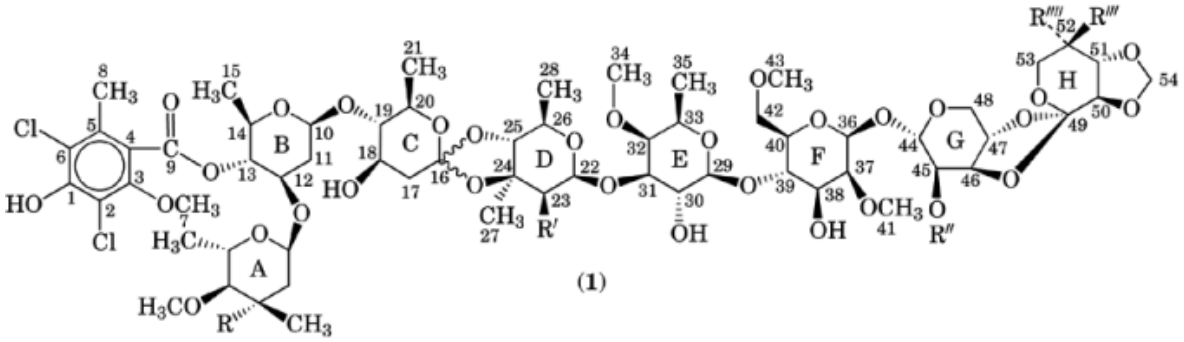
1. Properties

1.1. Physical Properties

Oligosaccharide antibiotics are colorless solids, which are often crystalline and have defined melting points and optical rotations, $[\alpha]_D$ (see Tables 1 and 2). They have a characteristic uv spectrum resulting from the phenolic ester residue, $\lambda_{max} \approx 285$ nm (ϵ ca 22), which shifts under basic conditions to $\lambda_{max} \approx 295$ nm (ϵ ca 80). The infrared spectrum shows absorptions for the hydroxyl and carbonyl moieties, and for other special features such as the nitro group which occurs at 1538 cm − 1. Molecular ions can be readily generated using modern mass spectral conditions such as fast atom bombardment (fab) (see Mass spectrometry) and the fingerprint fragmentation pattern has been employed for structure elucidation (8, 13, 14). X-ray analyses have been performed for the confirmation of partial structures of everninomicin (9, 16) and avilamycin (27). Modern

nmr spectroscopic methods have also contributed heavily to the structure assignments (see Magnetic spin resonance).

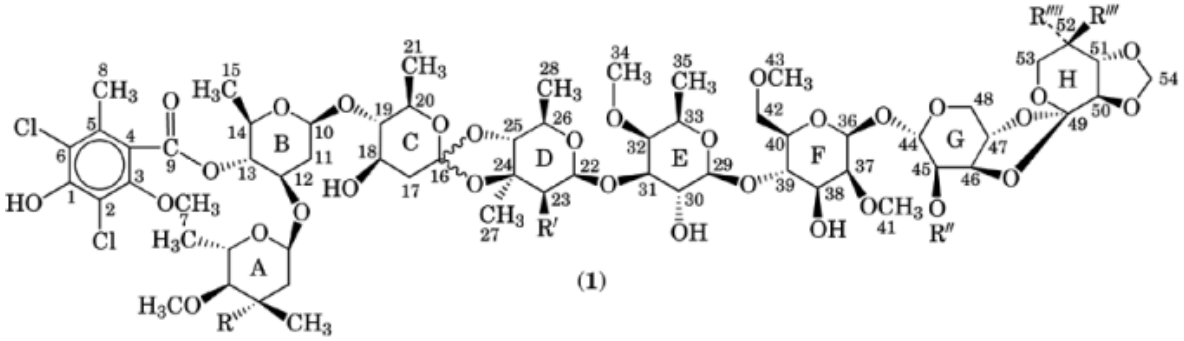
Table 1. The Everninomicins[a]



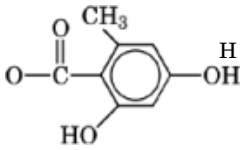
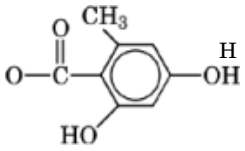
(1)

Compound	CAS Registry Number	Molecular formula	Mp, °C	$[\alpha]_D$	R	R′	R″	R‴	R⁗	Reference
everninomicin B	[53296-30-3]	$C_{66}H_{99}Cl_2NO_{36}$	184–185	−33.1	NO_2	OH	CH_3	(S)-CHOCH$_3$ / CH$_3$	OH	1
everninomicin C	[53296-29-0]	$C_{63}H_{93}Cl_2NO_{34}$	181–184	−33.7	NO_2	H	CH_3	OH	H	2
everninomicin D	[39340-46-0]	$C_{66}H_{99}Cl_2NO_{35}$	169–171	−34.2	NO_2	H	CH_3	(S)-CHOCH$_3$ / CH$_3$	OH	(3–11)
everninomicin 2	[116217-29-9]	$C_{58}H_{86}Cl_2O_{31}$	212–216	0.5	[b]	H	CH_3	(S)-CHOCH$_3$ / CH$_3$	OH	12
everninomicin 3	[64743-83-5]	$C_{66}H_{98}Cl_2O_{33}$	157–158	−29.8	[c]	H	CH_3	(S)-CHOCH$_3$ / CH$_3$	OH	11
everninomicin 7	[64597-16-6]	$C_{66}H_{100}Cl_2O_{34}$	173–175	−35.6	OH	H	CH_3	(S)-CHOCH$_3$ / CH$_3$	OH	11

Table 1. ***Continued***



(1)

Compound	CAS Registry Number	Molecular formula	Mp, °C	$[\alpha]_D$	R	R′	R″	R‴	R⁗	Reference
everninomicin-13-384-Component 1		$C_{70}H_{97}Cl_2NO_{38}$		−47.2	NO_2	OH	H			13
everninomicin-13-384-Component 5		$C_{70}H_{99}Cl_2NO_{36}$		−42.3	NH_2	OH	H			13

[a]The numbering is as in everninomicin (13).
[b]Ring A is absent in everninomicin 2, ie, Ring A = H.
[c]There is a double bond in everninomicin 3 at R.

1.2. Chemical Properties and Structure

Oligosaccharide antibiotics are sensitive to acid pH because of the ortho-ester linkages. Yet all of them have an acidic phenolic group which makes the molecule relatively unstable to handling conditions. The ortho-ester connecting the C and D rings (Table 1) is comparatively more sensitive to acid pH than the one linking the G and H residues. Other chemically reactive groups in these compounds are the glycosidic linkages, the hydroxyl and carbonyl groups, and any nitro groups present.

2. Everninomicins

Everninomicin D is the principal component from cultures of *Micromonospora carbonacae* (10). Its structure (5) was elucidated using extensive chemical degradation coupled with spectroscopic analysis and it was the first reported instance of a natural product containing a tertiary nitrosugar. X-ray analyses of both the olgose residue (9) and the nitrosugar (16) have been reported as has a complete mass spectral analysis of everninomicin D (8).

Chemical modification (6) of the nitro group in everninomicin D has resulted in the formation of amino, mono- and dialkylamino, *N*-acylamino, and *N*-hydroxylamino (3) (and its nitrone derivatives) everninomicin D, all of which possess great antibiotic activity (6) against gram-positive bacteria. Aminoeverninomicin D can be converted to the known (11) everninomicins 3 and 7 under buffered conditions (6). Electrochemical reduction (11) of nitro and nitroso everninomicin D also produced everninomicins 3 and 7. Phosphite reduction of nitroso everninomicin causes fragmentation of sugar residue A leading to everninomicin 2 (12).

Everninomicin B (1), though a secondary component, has been extensively investigated because of its improved pharmacokinetic properties over those of everninomicin D (3, 22). Everninomicin 13-384 Components 1 and 5, produced by *Micromonospora carbonacae* (24, 28) are newer members of the everninomicin family. The structures (13) were assigned through extensive use of nmr and fab ms techniques. As in everninomicin B, C, and D, 13-384 Component 1 has a nitrosugar, whereas Component 5 has an amino sugar in its place, shown by conversion of Component 1 to 5 by hydrogenation (13). ^{13}C nmr confirmed the characteristic ortho-ester carbon atoms at 119.2 and 120.4 ppm and an extra aromatic residue in ring H at C-52. Nmr and high resolution fab ms confirmed this aromatic residue to be the 2,4-dihydroxy-6-methylbenzoyloxy group. The two aromatic residues on either end of this molecule appear much closer in conformational proximity, as observed by nmr (13) in $CDCl_3$ solution. Chemical modification of Components 1 and 5 has provided a number of active derivatives (7).

3. Flambamycin, Curamycin, and Avilamycins

3.1. Flambamycin

Flambamycin, produced by *Streptomyces hygroscopicus* DS 23230, also has undergone substantial chemical degradative experiments during structure elucidation (22, 23, 25). Nmr interpretation of the structure was reported later (20, 26). The structure, shown in Table 2, chemical reactions, and biological properties have been thoroughly reviewed (22); it melts at 202–203°C.

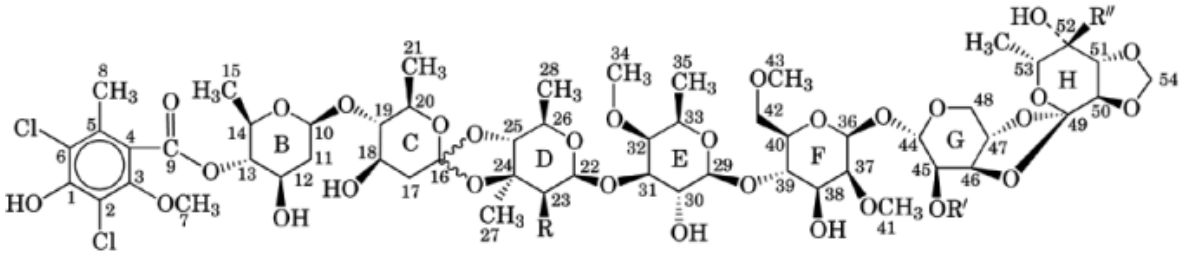
3.2. Curamycin

Curamycin A, presented in Table 2, is the primary component of the culture *Streptomyces curacoi* (21) and preliminary chemical degradation studies (18) established it to be an oligosaccharide antibiotic. Later when the complete structure was assigned (17, 19), the close relationship to flambamycin was evident. Curamycin A melts at 192–199°C.

3.3. Avilamycins

At least 16 avilamycins have been reported (14, 15, 29) and are listed in Table 2. Avilamycins A (mp 181–182) and C (mp 188–189) are the primary components (14) produced by the strain *Streptomyces viridochromogenes*. Structures have been established based on chemical degradation, nmr, and x-ray analysis. Structures for the rest of the compounds have been assigned based on nmr and fab ms (14) interpretations. Avilamycins F and H have only one chlorine atom in the phenolic ring. Relative hplc retention times for all the avilamycins have been recorded (14).

Table 2. The Avilamycins (R = H), Curamycin (R = H), and Flambamycin (R = OH).



(2)

Compound	CAS Registry Number	Molecular formula	R′	R″	References
avilamycin A	[69787-79-7]	$C_{61}H_{88}Cl_2O_{32}$	$COCH(CH_3)_2$	$COCH_3$	(14–17)
avilamycin A_1			$COCH_2CH_3$	H	
avilamycin B[a]	[73240-30-9]	$C_{59}H_{84}Cl_2O_{32}$	$COCH_3$	$COCH_3$	
avilamycin C[b]	[69787-80-0]	$C_{61}H_{90}Cl_2O_{32}$	$COCH(CH_3)_2$	$CH(OH)CH_3$	
avilamycin D_1	[82278-49-7]	$C_{57}H_{82}Cl_2O_{31}$	H	$COCH_3$	
avilamycin D_2			$COCH_3$	$CH(OH)CH_3$	
avilamycin E			H	$CH(OH)CH_3$	
avilamycin F[c]	[104748-55-2]	$C_{60}H_{87}ClO_{32}$	$COCH(CH_3)_2$	$COCH_3$	
avilamycin G	[104748-53-0]	$C_{62}H_{90}Cl_2O_{32}$	COC_4H_9	$COCH_3$	
avilamycin H[d]	[104748-54-1]	$C_{61}H_{89}ClO_{32}$	$COCH(CH_3)_2$	$COCH_3$	
avilamycin I	[104765-14-2]	$C_{60}H_{86}Cl_2O_{32}$	$COCH_2CH_3$	$COCH_3$	
avilamycin J[e]	[104748-48-3]	$C_{60}H_{86}Cl_2O_{32}$	$COCH(CH_3)_2$	$COCH_3$	
avilamycin K[f]	[104748-51-8]	$C_{61}H_{88}Cl_2O_{33}$	$COCH(CH_3)_2$	$COCH_3$	
avilamycin L	[104748-52-9]	$C_{60}H_{86}Cl_2O_{32}$	$COCH(CH_3)_2$	CHO	
avilamycin M[g]	[104748-50-7]	$C_{60}H_{86}Cl_2O_{32}$	$COCH(CH_3)_2$	$COCH_3$	
avilamycin N[h]	[104748-49-4]	$C_{60}H_{86}Cl_2O_{32}$	$COCH(CH_3)_2$	$COCH_3$	
curamycin A[i,a]	[73240-30-9]	$C_{59}H_{84}Cl_2O_{32}$	$COCH_3$	$COCH_3$	(18–21)
flambamycin	[42617-24-3]	$C_{61}H_{88}Cl_2O_{33}\cdot H_2O$	$COCH(CH_3)_2$	$COCH_3$	(22–26)

[a] Avilamycin B and curamycin A appear to be identical.
[b] $[\alpha]_D = -4.8$.
[c] Avilamycin F has an H at C-2.
[d] Avilamycin H has an H at C-6.
[e] Avilamycin J has an H in place of the C_{43} CH_3 group.
[f] Avilamycin K has a CH_2OH in place of the C_{35} CH_3 group.
[g] Avilamycin M has an H in place of the C_{35} CH_3 group.
[h] Avilamycin N has an H in place of the C_{41} CH_3 group.
[i] $[\alpha]_D = 5.3$.

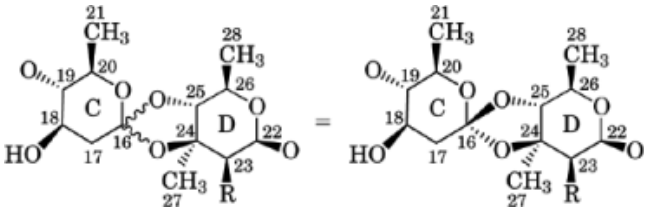


Fig. 1. Proposed ortho-ester configuration for ring C of the oligosaccharide antibiotics.

4. Other Oligosaccharides and Relevant Work

Sporacuracin A [58205-91-7], $C_{63}H_{94}Cl_2O_{35}$, mp 145–148°C, $[\alpha]_D - 26.3$, and sporacuracin B [58205-92-8], $C_{63}H_{94}Cl_2O_{35}$, mp 162–165°C, $[\alpha]_D - 18.8$, are other probable members of the oligosaccharide antibiotic family (22, 30).

In all of the oligosaccharides discussed herein the stereochemistry of the ortho-ester in ring C of C-16 has not as of this writing been unequivocally established. Based on mechanistic studies using simple model reactions, a proposal has been put forward (31) to define the possible configuration at the ortho-ester linkage of oligosaccharide antibiotics. Experimental evidence suggests that the axially oriented oxygen atom (Fig. 1) with respect to ring C undergoes cleavage under acidic pH. The total synthesis of curacin [20585-97-1], $C_{15}H_{18}Cl_2O_7$, corresponding to the A B ring fragment, has been reported (32) and has been compared to its synthetic regioisomer, isocuracin.

4.1. Biological Properties

The *in vitro* activity is such that oligosaccharides, in general, are highly potent, but are narrow-spectrum antibiotics (3, 4, 22). Everninomicins are active against a wide variety of gram-positive aerobes and anaerobes; *Neisseria*, *Mycoplasma*, and some *Mycobacteria*. These antibiotics are active against methicillin (see Antibiotics, penicillins and others): resistant *Staphylococci*, and compare to vancomycin (see Antibiotics, peptides). They lack cross-resistance with vancomycin because of different modes of action and their anaerobe activity is comparable to clindamycin (see ANTIBIOTICS, LINCOSAMINIDES). Everninomicin 13-384 Component 5 is said to have measurable *Pseudomonas* activity, but other members are devoid of any gram-negative activity. Comparatively, flambamycin is less potent than everninomicin D (22).

4.1.1. In Vivo Activity

Although highly active *in vitro*, everninomicin D posed pharmacokinetic problems when tested *in vivo* on mice and dogs. Everninomicin B, a close relative, on the other hand, gave better blood levels and *in vivo* efficacy. Similarly, Sch 23199,a semisynthetic *N*-acetyl analogue of everninomicin D also had useful activity and pharmacokinetic profile. In preliminary experiments in animals, everninomicin 13-384 Component 1 shows good *in vivo* activity. Finally, potential for use of oligosaccharide antibiotics in both human and animal health care has been claimed in various patents (7, 24, 28, 30, 33).

BIBLIOGRAPHY

"Antibiotics, Oligosaccharides" in *ECT* 3rd ed., Vol. 2, pp. 986–990, by A. K. Ganguly, Schering Corporation.

Cited Publications

1. A. K. Ganguly and A. K. Saksena, *J. Antibiot.* **28**, 707 (1975).
2. A. K. Ganguly and S. Szmulewicz, *J. Antibiot.* **28**, 710 (1975).
3. A. K. Ganguly, in P. Sammes, ed., *Oligosaccharide Antibiotics, Topics in Antibiotic Chemistry*, Vol. **2**, Ellis Horwood Publishers, Chichester, UK 1978, p. 49.
4. A. K. Ganguly, in M. Grayson, ed., *Oligosaccharides, Antibiotics, Chemotherapeutics, and Antibacterial Agents for Disease Control*, John Wiley & Sons. Inc., New York, 1982, p. 205.
5. A. K. Ganguly, O. Z. Sarre, D. Greeves, and J. Morton, *J. Am. Chem. Soc.* **97**, 1982 (1975).
6. A. K. Ganguly, V. M. Girijavallabhan, G. H. Miller, and O. Z. Sarre, *J. Antibiot.* **35**, 561 (1982).
7. U.S. Pat. 4,622,314 (Dec. 12, 1978), A. K. Ganguly, O. Z. Sarre, and V. M. Girijavallabhan (to Schering-Plough Corp.).
8. A. K. Ganguly and co-workers, *J. Antibiot.* **38**, 808 (1985).
9. A. K. Ganguly, O. Z. Sarre, A. T. McPhail, and K. D. Onan, *J. Chem. Soc. Chem. Commun.* **9**, 313 (1977).
10. M. J. Weinstein, G. M. Luedemann, E. M. Oden, and G. H. Wagman, *Antimicrob. Agents Chemother.* 24 (1964).
11. A. K. Ganguly and co-workers, *J. Chem. Soc. Chem. Commun.* **2**, 56 (1980).
12. A. K. Ganguly, S. Szmulewicz, O. Z. Sarre, and V. M. Girijavallabhan, *J. Chem. Soc. Chem. Commun.* **15**, 609 (1976).
13. A. K. Ganguly and co-workers, *Heterocycles* **28**, 83 (1989).
14. J. L. Mertz and co-workers, *J. Antibiot.* **39**, 877 (1986).
15. W. Keller-Schierlein, W. Heilman, W. D. Ollis, and C. Smith, *Helv. Chim. Acta* **62**, 7 (1979).
16. A. K. Ganguly, O. Z. Sarre, A. T. McPhail, and R. W. Miller, *J. Chem. Soc. Chem. Commun.* **1**, 22 (1979).
17. A. K. Ganguly, A. K. Bose, and N. F. Cappuccino, *J. Antibiot.* **32**, 1213 (1979).
18. E. G. Gros, V. Deulofeu, O. L. Galmarini, and B. Frydman, *Experientia* **24**, 323 (1968).
19. N. F. Capuccino, A. K. Bose, J. B. Morton, and A. K. Ganguly, *Heterocycles* **15**, 1621 (1981).
20. L. Valente and co-workers, *Tetrahedron Lett.* **13**, 1149 (1979).
21. O. L. Galmarini and V. Deulofeu, *Tetrahedron* **15**, 76 (1961).
22. D. E. Wright, *Tetrahedron*, Report No. 62, **35**, 1207 (1979).
23. W. D. Ollis, C. S. Smith, and D. E. Wright, *Tetrahedron* **35**, 105 (1979).
24. U.S. Pat. 4,735,903 (Apr. 5, 1988), J. A. Waitz and A. Horan (to Schering-Plough Corp.).
25. L. Ninet and co-workers, *Experientia* **30**, 1270 (1974).
26. W. D. Ollis and co-workers, *Tetrahedron* **35**, 993 (79).
27. E. Kupfer, K. Neupert-Laves, M. Dobler, and W. Keller-Schierlein, *Helv. Chim. Acta* **65**, 3 (1982).
28. U.S. Pat. 4,597,968 (July 1, 1986), J. A. Waitz and co-workers (to Schering-Plough Corp.).
29. F. Buzzetti and co-workers, *Experientia* **24**, 320 (1968).
30. Jpn. Pat. 75 125,094 (Oct. 1, 1975), A. Tamura and co-workers (to Dainippon) *J. Antibiot.*, Suppl. to Index 30, 77–111 and 77–112 (1977).
31. J-M Beau, G. Jaurand, J. Esnault, and P. Sinay, *Tetrahedron Lett.* **28**, 1105 (1987).
32. P. Jutten, J. Dornhagen, and H. Scharf, *Tetrahedron* **43**, 4133 (1987).
33. U.S. Pat. 4,436,734 (Mar. 13, 1984), E. E. Ose (to Eli Lilly Corp.).

V. M. GIRIJAVALLABHAN
Schering-Plough Corporation
ASHIT K. GANGULY
Schering-Plough Corporation

Related Articles

Antibiotics, introduction; Penicillins; Peptides