POLYETHER ANTIBIOTICS

1. Introduction

The polyether antibiotics were discussed by L. W. Crandall and R. L. Hamill in 1992 in the section on polyethers in the 4th ed. of the *Kirk-Othmer Encyclopedia of Chemical Technology*. The material presented in this original article has been included in this updated article.

The polyether antibiotics were first recognized as a separate class with the publication of the structure of monensin in 1967 (1). A major commercial use of these polyether antibiotics is the control of coccidiosis, a devastating disease of poultry. Their success can be attributed to the slow development of resistance to them by the parasites that cause the disease. A second commercial application, as growth promoters in ruminant animals, capitalizes on their antibiotic activities, which lead to improved feed conversion via manipulation of the rumen flora (see FEEDS AND FEED ADDITIVES). Compositions containing polyether antibiotics having reduced particle size and surface-acting agents are useful for protecting untanned animal hides from decomposition and for the preservation of hide quality (2).

These antibiotics are characterized by multiple tetrahydrofuran (THF) and tetrahydropyran rings connected by aliphatic bridges, direct C−C linkages, or spiro linkages. Other features include a free carboxyl function, many lower alkyl groups, and a variety of functional oxygen groups. These structural features enable the molecule to form a cyclic conformation with the oxygen functions at the center and the alkyl groups on the outer surface. This conformation results in lipid solubility, even for the salt forms, enabling transport of cations across lipid membranes. The potential for using these antibiotics as biochemical tools was recognized long before the structural features had been elucidated. Studies of antibiotics as inhibitors of mitochondrial enzymes (3) revealed the unique characteristics of nigericin and dianemycin, both later shown to be polyethers. The term ionophore was first used to describe compounds that can transport ions across artificial or natural membranes (4). The polyethers are sometimes referred to as carboxylic acid ionophores to distinguish these antibiotics from other compounds showing ionophoretic activity.

Individual polyethers exhibit varying specificities for cations. Some polyethers have found application as components in ion-selective electrodes for use in clinical medicine or in laboratory studies involving transport studies or measurement of transmembrane electrical potential (5,6). Membrane sensors have been developed for the direct detection of monensin and salinomycin in animal feed preparations in low levels 10−1000-μg / 5-g feed (7). Studies directed toward the design of a lithium selective electrode resulted in the synthesis of a derivative of monensin lactone that is highly specific for lithium (8). The ionophore properties of polyether antibiotics in large unilamellar vesicles is studied by ^{23}Na and ^{39}K NMR (9).

A new "biomimetic membrane transport" system mediated by monensin, lasalocid and salinomycin transports unnatural guest species such as amino acid ester salts, and heavy and transition metal cations, in their pseudocavities (10). The chiral recognition ability of polyether antibiotics as natural optically active host molecules has also been recognized (11,12). An example of this phe-

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nomenon is the molecular recognition of ferrioxamine B by host–guest complexation with lasalocid A (13).

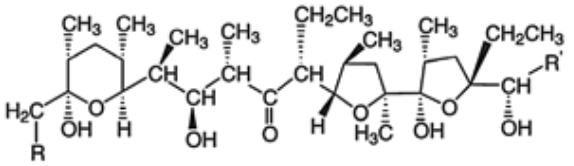
2. Properties

Although the rate of discovery has fallen relative to the 1970s there are now well over 120 naturally occurring fermentation-derived polyether ionophores known. A review published in 1995 includes the compounds whose structures were elucidated at that time (14).

A classification based first on ion specificity, then on structural features has been suggested for the polyethers (15). Another method uses the presence of unsaturation or aromatic groups in the molecular skeleton (16). In this article, the compounds are classified based on the number of carbons in the backbone according to the numbering system proposed in Ref. (17). The carbon backbone or skeleton refers to the longest chain of contiguous carbons between the carboxyl group and the terminal carbon.

Table 1 lists the polyether antibiotics arranged by the number of carbons in the skeleton. Many of these compounds were isolated independently in separate laboratories and thus have more than one designation. The groups are subdivided depending on the number of spiroketals. Two classes fall outside this scheme: the pyrrole ether type containing a heterocyclic ring, and the acyltetronic acid type, that has an acylidene tetronic acid instead of a carboxylic acid. These compounds are ionophores and because of their common features are included as polyethers.

Lysocellin (1, R = COOH, R′ = CH_2CH_3), X14889 A (1, R′ = R = CH_3), and X14889 C (1, R = COOH, R′ = CH_3) are examples of the shortest polyethers, those having 22 carbons in the backbone. X14889 A, a minor factor, is atypical in that it does not contain a carboxylic acid. The 24 carbon backbone group includes the commercially important lasalocid A (2), one of the first polyethers to be isolated. Monensin A (3, R′ = CH_3, R = CH_2CH_3, R″ = H), another widely used anticoccidial and feed efficiency enhancer, has one spiroketal and a 26 C backbone. Other closely related members of this subgroup are monensin B (3, R′ = R = CH_3, R′ = H) and laidlomycin (3, R = $COCH_2CH_3$, R′ = CH_3, R″ = H). The propionyl ester of laidlomycin [84799-02-0] (3, R = R″ = $COCH_2CH_3$, R′ = CH_3), $C_{40}H_{66}O_{13}K$, is currently at the preregistration stage of development for use as a feed additive.



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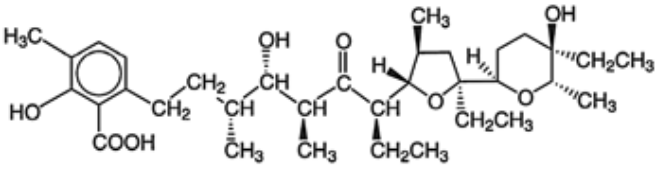

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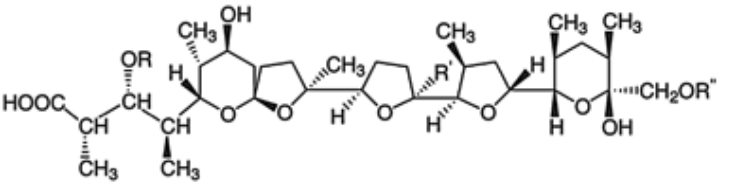
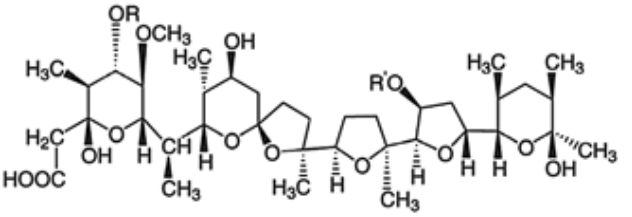


(3)

The C-30 skeleton group accounts for $\sim$ 60% of the polyethers for which structures have been determined. Most of these contain a sugar moiety, usually 2,3,6-trideoxy-4-*O*-methyl-D-erythropyranose [65104-53-2]. The single spiroketal subset is illustrated by two closely related compounds, semduramicin (4, R = H, R′ = 5) and maduramicin alpha (4, R = CH_3, R′ = 6). Maduramicin is marketed as an anticoccidial and semduramicin is under development for the same application.



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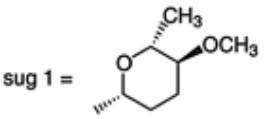

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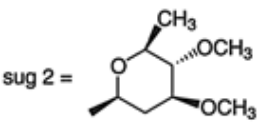
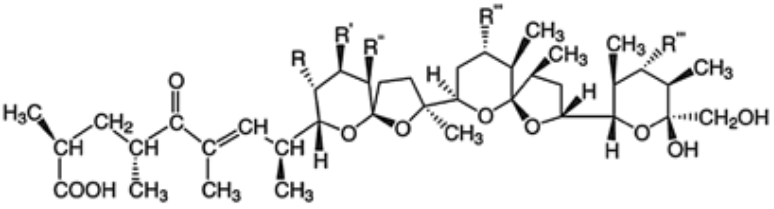


(6)

The group containing two spiroketals is also characterized by an alpha–beta unsaturated ketone. Representative structures are illustrated by CP53607 (7, $R = CH_3$, $R' = OH$, $R'' = R''' = R'''' = H$), which has no sugar, dianemycin (7, $R = CH_3$, $R' = OH$, $R' = R'''' = H$, $R''' = 8$), which has one sugar, and A130 B (7, $R = R''' = H$, $R' = R'''' = 8$, $R'' = CH_3$), which has two sugars.



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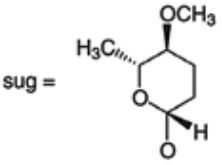

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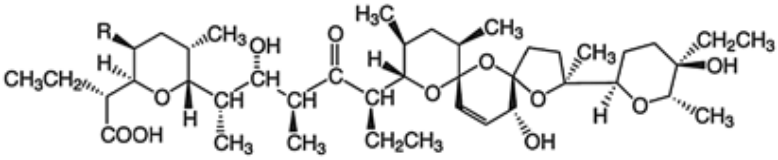
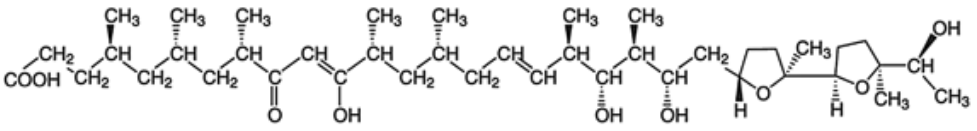
Two commercially important polyethers, narasin (9, $R = CH_3$) and salinomycin (9, $R = H$) have an unusual trispiroketal linkage.



(9)

Ionomycin (10), a 32 C, 0-spiroketal, has a profound specificity for Ca^{2+} and is an important biochemical tool. The beta-carbonyl moiety provides a second charged ligation point, enabling this compound to form 1:1 complexes with divalent cations.



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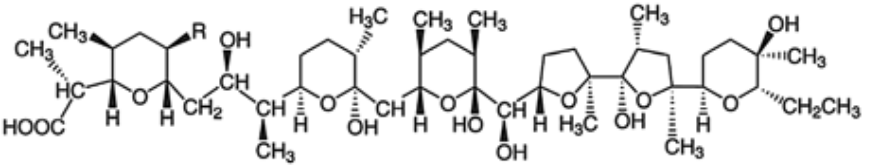
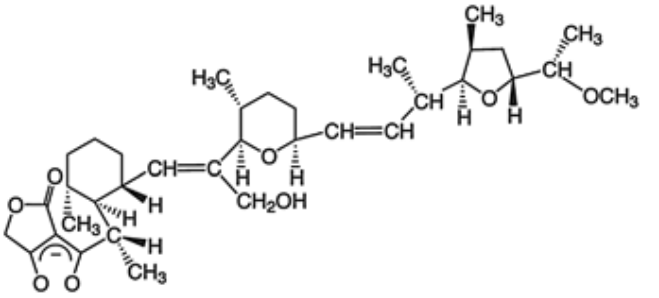
X206 (11 , R = H) and alborixin (11, R = CH_3) are the only known representatives of the 37 C backbone subset.



(11)

Tetronasin (12) is an example of the acyl tetronic acid class and A23187 (13, R = $NHCH_3$, R′ = R″ = CH_3) and related compounds, CP61405 (13, R = OH, R′ = R″ = H), X14885 A (13, R = OH, R′ = CH_3, R″ = H), and AC7230 (13, R = OH, R′ = R″ = CH_3) are examples of the pyrrole ether group.



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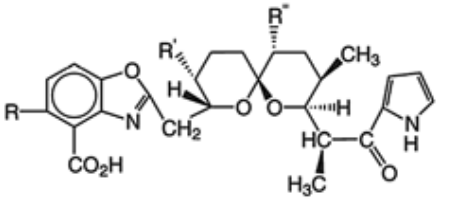

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3. Purification and Production

Polyethers are usually found in both the filtrate and the mycelial fraction, but in high yielding fermentations they are mostly in the mycelium because of their low water solubility (182). The high lipophilicity of both the free acid and the salt forms of the polyether antibiotics lends these compounds to efficient organic solvent extraction and chromatography on adsorbents such as silica gel and alumina. Many of the production procedures utilize the separation of the mycelium followed by extraction using solvents such as methanol or acetone. A

number of the polyethers can be readily crystallized, either as the free acid or as the sodium or potassium salt, after only minimal purification.

Polyethers such as monensin, lasalocid, salinomycin, and narasin are sold in many countries in crystalline or highly purified forms for incorporation into feeds or sustained-release bolus devices (see CONTROLLED-RELEASE TECHNOLOGY). There are also mycelial or biomass products, especially in the United States. The mycelial products are generally prepared by separation of the mycelium and then drying by azeotropic evaporation, fluid-bed driers, continuous tray driers, flash driers, and other types of commercial driers (183). In countries allowing biomass products, crystalline polyethers may be added to increase the potency of the product.

Polyether production is improved by the addition of fatty acids and detergents. Addition of pure methyl oleate to a *S. hygroscopicus* NRRL B-1865 culture improved the production of nigericin and abierixin (184). Polyether biosynthesis in actinomycetes is regulated at the level of precursor supply by effects of nutrients on the sources of the low molecular weight fatty acids used to build the carbon framework of these molecules (185).

4. Analysis

Methods for the general detection of polyether antibiotics have been reviewed (186) and a critical review provides information on practical and legislative aspects on analytical methods for the detection of polyether ionophore residues in poultry (187). Simultaneous detection of several polyether antibiotics in poultry feeds and residues is carried out by liquid chromatography with ultraviolet (uv) detection after derivatization with 2,4-dinitrophenylhydrazine (188) or with fluorescence detection by derivatization with 1-bromoacetylpyrene (189). Microbore high performance liquid chromatography (HPLC) determination of polyether antibiotics using postcolumn derivatization with benzaldehyde reagents is also a method for detection of polyether antibiotics in premixes and feeds (190). A simple method using solid-phase extraction (SPE) and liquid chromatography–mass spectrometry (LCMS) with electrospray ionization can be used for the detection of narasin, salinomycin and monensin in liver from domestic foul (191).

Classical microbiological methods for determining antimicrobial compounds in feeds are nonspecific therefore bioautography is used to identify biological activity. The method involves agar diffusion of buffered samples into several test bacteria, a neutral extraction of polyether antibiotics followed by thin-layer chromatography (TLC), and an acid extraction for other antibiotics. Identification after TLC is achieved by bioautography with the most sensitive microorganism(s) (192). The TLC/bioautographic analysis is also used for analysis of polyether antibiotic residues in poultry meat (193). A monoclonal-based enzyme-linked immunosorbent assay (ELISA) kit provides a rapid test for monensin (194).

5. Biological Activities

The polyether antibiotics exhibit a broad range of biological, antibacterial, antifungal, antiviral, anticoccidial, antiparasitic, and insecticidal activities. They improve feed efficiency and growth performance in ruminant and monogastric animals. The anticoccidial activity in poultry and cattle, and the effect on feed efficiency in ruminants such as cattle and sheep are of commercial interest.

Polyether antibotics have been observed to control Gram-positive bacteria in the industrial extraction of sugar products (195) and mollusks, such as *Lymnaeidae* that are present in municipal wastewater-treatment tanks (196).

Table 2 gives antimicrobial data for representative polyethers. In general, the polyethers are effective against Gram-positive and anaerobic bacteria, but in general are less effective against Gram-negatives (197). Polyether antibiotics do however, control the growth of the Gram-negative bacteria *Helicobacter pylori*, an agent associated with disorders of the gastrointestinal tract (198). Monensin exhibits in vitro bacteriostatic activity against an isolate of *Legionella pneumophila* (199).

The antibacterial properties play an important, though poorly understood, role in the improvement of feed efficiency in ruminants (200). High toxicity has limited the use of these compounds as antibacterial and antifungal agents. The toxicity varies somewhat from species to species, and the commercial polyethers are well tolerated in poultry and cattle at the use level. While ionophore comparative toxicity is difficult to estimate, a cross-comparison study indicated the relative toxicities of the ionophores from lowest to highest were salinomycin<lasalocid≤narasin≤monensin (but lasalocid<monensin)<maduramycin (201). Horses are subject to lethal toxicity at relatively low (1–2 mg/kg) dosages (202).

Treponema hyodysenteriae, a causative agent of swine dysentery, is sensitive to polyether antibiotics at low concentrations *in vitro*. In pigs, lasalocid was effective in controlling dysentery at levels of 0.005–0.05% in feeds (203). Salinomycin is also effective in controlling *Clostridium perfringens* type-A infection in growing pigs when administered at the registered dose range for use as a performance enhancer (204). Several species of Mycoplasma are inhibited *in vitro* at a MIC range of 2.0–25 μ/mL of polyethers including narasin, carriomycin, and K41 (197).

Laidlomycin was found to be the most potent polyether antibiotic to reverse colchicine resistance in multidrug resistant human carcinoma KB-C4 cells (205).

5.1. Antiviral Activity. Tissue culture studies have demonstrated activity against a wide range of viruses including the veterinary pathogens, transmissible gastroenteritis virus, infectious canine heptatitis, Newcastle disease virus, infectious bovine rhinotracheitis, and pseudorabies (206). Monensin, narasin, septamycin, and nigericin were effective in treating an infection of transmissible gastroenteritis virus in piglets at doses of 0.1–100 mg/kg (206). The mechanism of inhibition has not been characterized, but it is probably related to the ionophoretic properties of these antibiotics. Monensin has been shown to inhibit the intracellular transport of viral membrane proteins of cells infected with Semliki Forest virus (207). The formation of syncytia, normally observed when T-

lymphoblastoid cell line (CEM) cells are cocultivated with human immunodeficiency virus (HIV-1)-infected T-cell leukemia cell line (MOLT-3) cells, was significantly inhibited in the presence of monensin (208). This observation suggests that the viral glycoproteins in the treated cells were not transported to the cell surface from the Golgi membrane. Several polyether antibiotics also exhibited inhibitory activity in cultures of monocytic lineage U937 cels chronically infected with human immunodeficiency virus (HIV) type 1 (209).

In Bulgaria, a preparation containing nigericin is used topically as an antiherpes drug (210).

5.2. Antimalarial Activity. The ionophore properties of cationomycin and monensin were studied on human erythrocytes by measuring sodium ion influx by ^{23}Na NMR together with potassium ion efflux by potentiometry in the presence of increasing amounts of serum. Parallel measurements of IC_{50} values for 50% growth inhibition of *Plasmodium falciparum*, one agent for malaria, revealed a correlation between the ion transport currents and the the IC_{50} value (211). Antibiotic X-206 exhibits potent *in vivo* antimalarial activity in a rodent model (212).

5.3. Anticoccidial Activity. The 1968 report that claimed monensin has activity against *Eimeria sp.*, particularly *E. tenella*, greatly altered the prevention and control of coccidiosis in poultry (46). It is estimated that the polyether ionophores presently constitute $> 80\%$ of the total worldwide usage of anticoccidials (213). Lasalocid and monensin have been approved for use in control of coccidiosis in cattle. To combat more tolerant, ie, resistant coccidia, particularly *E. acerulina* and *E. maxima*, a 1:1 combination of narasin and nicarbazin, eg, 0.45-kg premix containing 36 g of each compound, has been marketed as Maxiban by Elanco. These two compounds work synergistically against less susceptible field strains. No new anticoccidial agent has come onto the market in the 1990s which is a reflection of the level of success that ionophores have brought to the control of the disease.

The ionophoretic properties of polyether antibiotics are important in their mode of action against coccidia (214). The primary coccidicidal effect of monensin involves an influx of sodium ions which results in swelling and vacuolization of the parasite because of osmotic pressure effects. A secondary effect is the stimulation of glycolysis on the part of the parasite resulting in a depletion of carbohydrate stores and eventual death. *Toxoplasma sp.*, coccidia related to *Eimeria sp.*, are infective in humans by two routes: fecal-oral ingestion of oocysts from the definitive host, the cat; and ingestion of tissue cysts from the intermediate host through eating undercooked meat such as lamb or pork. Low concentrations of nigericin (0.05 mg/mL) totally inhibit the intracellular development of tachyzoites of *Toxoplasma gondii* (215). Monensin has been shown to be effective against toxoplasmosis in cats (216) and sheep (217).

Ionophores are widely used by the poultry industry and are unique in that they permit a small "leakage" of coccidia to enable the bird to develop a certain level of immunity. This allows a greater degree of protection against the parasite and is a more efficient method of control. In the first few weeks or days of life, the immune system is not developed. Protection in the early stage is often provided by a chemical agent and followed by a switch to an ionophore. Such "shuttle programmes" provide a balance between control of infection and development of

immunity in the older bird. Other authorities are known to propose a "reverse" shuttle where the starting anticoccidial is an ionophore followed by a chemical based product (218). Between 1995 and 1999, eg, ~ 40 different drug programs were utilized in broiler production in the United States (219). These range from programs using a single drug to programs using different drugs in the various poultry feeds (shuttle programs). The development of resistance to inophorous anticoccidials has been comparatively slow. However, increasing resistance problems have been noticed in many countries (220).

5.4. Enhancement of Feed Efficiency in Ruminants. Polyether antibiotics have been shown to improve feed efficiency in ruminant animals such as cattle, sheep, and goats and also to enhance weight gain. This enhancement in growth performance has been shown to correlate with increased production of propionic acid in the rumen. A decrease in the production of acetic acid, butyric acid, and methane often accompanies the increased propionic acid production. These volatile fatty acids (VFA) are produced in the rumen by the degradation of carbohydrates by microorganisms. The polyethers apparently selectively inhibit certain of the microorganisms to achieve greater propionate production. Propionate is thought to be more effectively utilized in energy metabolism in the host animal than acetate or butyrate. The effect on production efficiency and mode of action has been reviewed (221,222) (see also GROWTH REGULATORS).

Because feed comprises > 80% of the cost of producing and fattening cattle, the maximum utilization of ever increasingly expensive rations is of upmost importance (223). Monensin under the trade name of Rumensin (Elanco Products) was introduced in 1976 at a recommended level of 30 ppm in cattle feed. Lasalocid having the trade name Bovatec® (Hoffmann-LaRoche, Inc.) was marketed some years later.

Salinomycin (224) and narasin (148) have been reported to be effective in improving feed efficiency but neither has been marketed for this use. Laidlomycin propionate (Syntex, Inc.) and tetronasin (Coopers Animal Health, Inc.) have been under investigation in cattle and sheep (225,226).

The polyethers have been reported to increase growth performance in monogastric animals such as horses, swine, and rabbits. No commercial use has been approved for swine diets. The sensitivity of horses to the toxic effects of these antibiotics precludes consideration of their use.

6. Biosynthesis

Bacteria belonging to the order Actinomycetales are the organisms reported to produce all of the polyethers. Most are secondary metabolites of Streptomyces sp. with the species hygroscopicus and albus accounting for about one-third of the antibiotics. Other genera represented are Streptoverticillium, Dactylosporangium, Actinomadura, Nocardia, and Nocardiopsis. The taxonomy of these producing organisms has been reviewed (227).

As is the case in other antibiotic families, the polyethers are often produced as complexes of closely related compounds. For example, lasalocid A is the principal component in a six-membered complex from Streptomyces lasaliensis; NRRL 3382 (29) and leuseramycin are coproduced also with four minor factors

from Streptomyces hygroscopicus ATCC 31590 (139,141). The use of isotopically labeled substrate and subsequent analysis of the labeling patterns have established the polyketide route as the principal pathway for biosynthesis (228,229). The shortest polyether, lysocellin, is constructed from 11 short-chain fatty acid units, whereas the longest, X-206 and alborixin, are assembled from 18 subunits. Most, however, are assembled from 15 subunits giving the C-30 backbone. After cyclization of the ether rings the molecules can be modified by the addition of methyl groups or sugar moieties.

The Cane-Celmer-Westley unified stereochemical model is an elegant proposal relating the stereochemistry of 30 different polyethers (230). According to this hypothesis, the cyclic ether groups arise by a cascade of cyclization steps on a polyepoxide intermediate, which arises from a polyene precursor having double bonds in the (*E*)-configuration. The first direct support for the polyene-polyepoxide concept was obtained through the incorporation of ^{13}C and ^{18}O doubly labeled precursors into the polyethers monensin (231) and lasalocid A (232). The only oxygenated centres not enriched were at positions predicted to arise from O_2. Subsequently, however, putative triene intermediates for the biosynthesis of monensin were synthesized but no incorporation of these compounds into monensin A or B were found (233). Biosynthetic studies employing ^{18}O-labeled precursors have also been reported for the polyethers salinomycin, narasin, maduramycin, lenoremycin and ICI139603 (234).

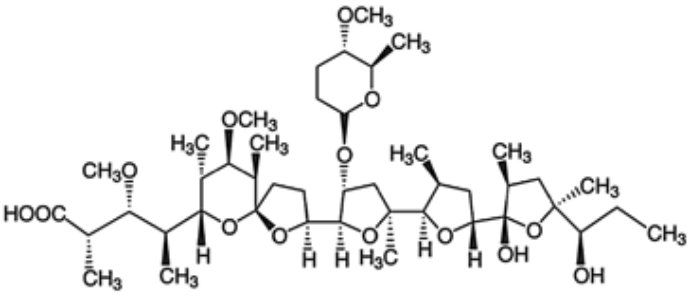
The first general model (230) for the biosynthesis of polyether antibiotics proposed late stage oxygenation of a complete carbon chain polyalkene followed by polyepoxidation and subsequent tandem anti-cyclization of a hydroxyepoxide. An alternative mechanistic model for polyether biosynthesis via tandem, hydroxyl-directed syn-oxidative polycyclization of a hydroxypolyene has also been proposed (235,236).

Biosynthesis of polyether antibiotics is catalyzed by a large family of polyketide synthases (PKSs) that function in a similar manner to fatty acid synthase using malonyl-CoA, methylmalonyl-CoA and ethylmalonyl-CoA as extender units for building the polyketide backbone (237–239). Many gene clusters encoding the enzymes of polyketide biosynthesis have been cloned and characterized (240), and combinatorial biosynthesis using actinomycete PKSs has led to the production of many “unnatural natural products” (241–243).

7. Structure Determination and Synthesis

Because of the complexity of the polyether antibiotics, little progress has been made in structure determination by the chemical degradation route. The ability of polyether antibiotics to chelate metal ions and form stable crystalline salts has facilitated structure elucidation by X-ray analysis and this has been the technique of choice for the study of many of these ionophores. Monensin, X206, lasalocid, lysocellin, and salinomycin were included in 19 distinct polyether X-ray analyses reported in 1983 (244). A recent addition is antibiotic CP44,161 (245). Use of MS (246), and ^{1}H (247) and ^{13}C NMR (161) are also reviewed. More innovative developments in these latter techniques have resulted in increased applications for structure determinations. For example, heteronuclear multiple bond

connectivity (HMBC) and homonuclear Hartmann-Hahn spectroscopy were used to solve the structure of portimicin (14). Scientists at Pfizer have now refined the use of NMR studies such that predictions can be made about an unknown ionophore structure based solely on NMR data. These are known as "Whipple's rules" after their originator (31). The conformational analysis of the sodium salt of monensin using long range C–H coupling constants indicated the conformations of the sodium salt of monensin in solvents were different from those in the crystal (248). Fast atom bombardment MS has also been used to solve the structures of several polyether antibiotics (249) including maduramicin α and cofactors (68) and *O*-demethylabierixin (250).



(14)

The framework of these molecules dominated by the presence of tetrahydrofurans, tetrahydropyrans, spiroacetals and bis(spiroacetals) presents challenging synthetic targets that require a high degree of stereo-, regio-, and chemoselectivity for each step. The synthesis of polyether antibiotics was initially reviewed in 1983 (251), and a recent review summarizes the advances in strategy and methods that have been developed to prepare 16 members of this class of complex natural products (252). This latter review discusses (in chronological order) the elegant total syntheses of lasalocid A, isolasolocid A, monensin A, calcimycin A, indanomycin, zincophorin, X-206, narasin, salinomycin, ionomycin, ferensimycin B, routiennocin, lysocellin, tetronomycin, tetronosin, and lonomycin.

The total synthesis of these complex molecules provides an excellent vehicle for the development of new methods for polypropionate synthesis including the use of chiral enolates as a versatile method to construct propionate units efficiently. The use of allylic 1,3 strain (A-1,3) by Kishi allows the synthesis of propionate fragments and tetrahydrofuran formation by hydroboration, epoxidation, and haloetherification. The use of Sharpless asymmetric epoxidation and dihydroxylation further extends these transformations to provide enantiomerically pure propionate fragments. Assembly of propionate fragments is also effected using Cram and Cram-chelation controlled addition of nucleophiles to carbonyl groups. A recent synthesis of ionomycin also demonstrates the utility of ring-opening methodologies in the synthesis of polypropionate and deoxypolypropionate subunits (253).

A total synthesis of ionomycin utilizes a novel sulfur-assisted organocuprate displacement of a secondary tosylate with complete inversion of configuration (254). A synthesis of zincophorin utilizes the hetero-Diels-Alder reaction for

the synthesis of both the polyol and pyran portions of the molecule (255,256). The Ireland ester enolate Claisen rearrangement provides an effective method for construction of key bonds in the total syntheses of lasalocid (257), monensin (258) and indanomycin (259,260). Methods for construction of the unusual bis (spiroacetal) core unit in salinomycin and narasin have been summarized elsewhere (261) and include the use of a novel oxidative rearrangement of an acyl furan (262).

8. Economic Aspects

In 1992, the worldwide usage of polyether antibiotics for controlling coccidiosis was approximately US$190 million compared to a total market of US$210–220 million. Monensin and salinomycin represent $\sim$ 65–70% of this market; lasalocid, narasin, and maduramicin make up the remainder. Other compounds for coccidiosis control include nicarbazine, halofunginone, amprolium, and robenidine. Worldwide usage is in excess of 3 million kg of product. The total world market for the use of ionophores for feed efficiency improvement in ruminants is $\sim$ $80–90 million.

The primary manufacturers are Hoffmann-LaRoche, Inc., Pfizer, Inc., Agri-Bio Corp. (a division of A. H. Robins), Elanco Products Co. (a division of Eli Lilly and Co.), Hoechst-Roussel, Agri Vet Co., American Cyanamid Co., and Kaken Pharmaceutical Co. Table 3 lists the polyether antibiotics approved by the US FDA for use as anticoccidial drugs in poultry. Lasalocid and monensin have also been approved by the US FDA for use in bovine coccidiosis at levels in feed of 11–33 g/t.

United Kingdom sales of coccidiostats for use in poultry between 1993 and 1999 (263) decreased for several reasons—the implementation of multifaceted preventive medicine programs, increased efforts to reduce production costs, enhanced focus on residue avoidance, and rapid production of efficacious vaccines by manufacturers. Vaccines to prevent coccidiosis are available and are used in replacement/breeding stock. A vaccine for routine use in broilers has also been launched. Future use of polyether antibiotics for the treatment of coccidiosis is therefore in conjunction with the use of vaccines.

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Table 1. **Polyether Antibiotics**

Name[a]	CAS Registery number	Molecular formula	Producing organism	Mp, °C	Reference I[b]	Reference S[c]
22–23 Carbon backbone (22C,23C), 0-Spiroketal						
ferensimycin A (5057 A)	[83852-59-9]	$C_{34}H_{60}O_{10}$	*Streptomyces* sp. 5057 FERM BP-62	133–135	18	18
ferensimycin B (5057 B)	[83852-60-2]	$C_{35}H_{62}O_{10}$	*Streptomyces* sp. 5057 FERM BP-62	143–145[d]	18	18
lysocellin (X14537 A)	[55898-33-4]	$C_{34}H_{60}O_{10}$	*Streptomyces cacaoi* var. *asoensis, Streptomyces longwoodenis* ATCC 29251	158–160[d]	19,21	20
X14873 A	[88263-37-0]	$C_{35}H_{62}O_{11}$	*Streptomyces* sp. X 14873 ATCC 31679	154[d]	22	22
X14873 G	[88263-35-8]	$C_{34}H_{60}O_{8}$	*Streptomyces* sp. X 14873 ATCC 31679	152–153	22	22
X14873 H	[88263-36-9]	$C_{34}H_{62}O_{9}$	*Streptomyces* sp. X 14873 ATCC 31679	145–146	22	22
X14889 A	[97671-96-0]	$C_{33}H_{60}O_{8}$	*Streptomyces* sp. X 14889 NRRL 15517	149–150	23	23
X14889 C	[97671-95-9]	$C_{33}H_{58}O_{10}$	*Streptomyces* sp. X 14889 NRRL 15517	139–141[d]	23	23
X14889 D	[97671-94-8]	$C_{33}H_{58}O_{7}$	*Streptomyces* sp. X 14889 NRRL 15517	117	23	23
CP-101,765	[142058-22-8]	$C_{36}H_{58}O_{8}$	*Streptomyces* sp. ATCC 55027	160–162	24	24
24 C, 0-Spiroketal						
inostamycin	[129905-10-8]	$C_{38}H_{68}O_{11}$	*Streptomyces* sp. MH816-AF15	181[d]	25	25
isolasalocid A	[54156-67-1]	$C_{34}H_{54}O_{8}$	*Streptomyces lasaliensis* NRRL 3382	185[d]	26	26
lasalocid A (X537 A)	[25999-31-9]	$C_{34}H_{54}O_{8}$	*S. lasaliensis* NRRL 3382	100–109	27	28
lasalocid B	[55051-86-0]	$C_{35}H_{56}O_{8}$	*S. lasaliensis* NRRL 3382	86–87	29	29
lasalocid C	[55051-84-8]	$C_{35}H_{56}O_{8}$	*S. lasaliensis* NRRL 3382	97–100	29	29
lasalocid D	[55051-82-6]	$C_{35}H_{56}O_{8}$	*S. lasaliensis* NRRL 3382	102–104	29	29
lasalocid E	[55051-80-4]	$C_{35}H_{56}O_{8}$	*S. lasaliensis* NRRL 3382	90	29	29
24 C, 1-Spiroketal						
CP-54,883	[112396-63-1s]	$C_{41}H_{61}Cl_2O_{12}$	*Actinomadura routienii* Huang N365-41	330–340[d]	30	31

25 C, 0-Spiroketal						
CP-78,545	[124150-86-3]	$C_{33}H_{58}O_7$	*Streptomyces* sp. N731-45	94–98	32	32
zincophorin (Griseochelin, M144255)	[91920-88-6]	$C_{33}H_{60}O_7$	*Streptomyces griseus* NCIB 11504, ZIMET	66–70	33,34	33,35
26 C, 1-Spiroketal						
CP-47,433	[74758-62-6]	$C_{47}H_{82}O_{14}$	*Actinomadura macra* ATCC 31286	89–99	36	37
CP-47,434	[74758-61-5]	$C_{46}H_{80}O_{14}$	*A. macra* ATCC 31286	230–238[d]	36	37
CP-80,585	[128345-23-3]	$C_{37}H_{64}O_{11}$	*Streptomyces* sp. ATCC 53862		38	38
CP-82,996	[127288-12-4]	$C_{50}H_{86}O_{16}$	*Actinomadura* sp. ATCC 53764	115–117	39	39
deoxylaidlomycin (A712)	[102674-88-4]	$C_{37}H_{62}O_{11}$	*Streptoverticillium eurocidicum* SANK 61484	194–196[d]	40	40
			Streptoverticillium olivoreticuli IMET 43861		41	
laidlomycin (AB78, TS822)	[56283-74-0]	$C_{37}H_{62}O_{12}$	*S. eurocidium* ATCC 31175, *Streptomyces olivoreticuli* A14939	151–153	42,43	43, 44
26-deoxymonensin	[122576-59-4]	$C_{36}H_{62}O_{10}$	*Streptomyces cinnamonensis* ATCC 15413		45	45
monensin A	[17090-79-8]	$C_{36}H_{62}O_{11}$	*S. cinnamonensis* ATCC 15413	103–105	46	1
monensin B	[30485-16-6]	$C_{35}H_{60}O_{11}$	*S. cinnamonensis* ATCC 15413	227–228[d]	46	47
monensin C	[1980-87-7]	$C_{37}H_{64}O_{11}$	*S. cinnamonensis* ATCC 15413	212–214[d]	46	47
27 C, 1-Spiroketal						
6270 B	[122548-05-4]	$C_{44}H_{74}O_{13}$	*Nocardiopsis* sp. FERM BP-717		48	48
A82810 (CP-84,657)	[127759-24-4]	$C_{45}H_{78}O_{14}$	*Actinomadura fibrosa* NRRL 18348, *Actinomadura* sp. ATCC 53708	255–257[d]	49,50	49,50
cationomycin	[82987-42-6]	$C_{45}H_{70}O_{15}$	*Actinomadura azurea* FERM BP-83	108–112	51	51
kijimicin	[129297-22-9]	$C_{37}H_{64}O_{11}$	*Actinomadura* sp. MI215-NF3	217–218[d]	52	52
portmicin (A80190)	[103521-25-1]	$C_{44}H_{76}O_{14}$	*Nocardiopsis* sp. 6270 FERM BP-7171, *Actinomadura oligospora* NRRL 15878	115–118	53,54	54,55
30 C, 0-Spiroketal						
UK41637	[83532-94-9][d]	$C_{46}H_{78}O_{16}$	*Actinomadura cremea* ATCC 31676	196–198[d]	56	56

Table 1. (***Continued***)

Name[a]	CAS Registery number	Molecular formula	Producing organism	Mp, °C	Reference I[b]	Reference S[c]
30 C, 1-Spiroketal						
6016	[69421-39-2]	$C_{46}H_{78}O_{16}$	*Streptomyces albus* 6016	192–195[d]	57	58
A204 A	[43110-10-7]	$C_{49}H_{84}O_{17}$	*S. albus* NRRL 3384	96–98	59	60
A204 B	[65208-37-9][d]		*S. albus* NRRL 3384		59	[e]
A28695 B	[42617-35-6]	$C_{49}H_{82}O_{17}$	*S. albus* NRRL 3883	122–124	61	62
A80438 (demethoxylonomycin A, SF2437)	[108044-86-6]	$C_{43}H_{74}O_{13}$	*Streptomyces pactum* NRRL 15970, *Streptomyces bobili* NRRL 15971, *Streptomyces* sp. FERM P-8469	160–162[d]	63,64	63,65
abierixin	[100634-16-0]	$C_{40}H_{68}O_{11}$	*S. albus* NRRL B-1865	83–85	66	66
BL580 beta	[53414-72-5]	$C_{47}H_{80}O_{16}$	*S. hygroscopicus* NRRL 5647		67	68
BL580 delta	[66389-75-1]	$C_{47}H_{80}O_{16}$	*S. hygroscopicus* NRRL 8180	157–161[d]	69	70
carriomycin (T42082)	[65978-43-0]	$C_{47}H_{80}O_{15}$	*S. hygroscopicus* ATCC 31080	120–122	71	72
CP-70,228	[101621-31-2]	$C_{53}H_{90}O_{18}$	*Actinomadura roseorufa* ATCC 39697	113–123	73	73
CP-70,828	[101621-30-1]	$C_{54}H_{92}O_{18}$	*A. roseorufa* ATCC 39697	133–136	73	73
UK-58852	[182364-81-4]	$C_{52}H_{88}O_{17}$	*A. roseorufa* ATCC 39697		74	74
octacyclomycin	[98824-17-0]	$C_{52}H_{88}O_{19}$	*A. roseorufa* ATCC 39697		75	75
CP-91,243	[135179-21-4]	$C_{50}H_{84}O_{18}$	*A. roseorufa* ATCC 53666		76	76
CP-91,244	[135215-73-5]	$C_{51}H_{86}O_{18}$	*A. roseorufa* ATCC 53666		76	76
CP-82,009	[135215-73-5]	$C_{49}H_{84}O_{17}$	*Actinomadura* sp. ATCC 53676	95–102	77	77
2-epi-mutalomycin	[124918-41-8]	$C_{41}H_{70}O_{12}$	*Streptomyces mutabilis* NRRL 8086	166–167[d]	78	78
28-epi-mutalomycin	[124986-36-3]	$C_{41}H_{70}O_{12}$	*S. mutabilis* NRRL 8086	187–191[d]	78	78
epi-nigericin	[108266-17-7]	$C_{40}H_{68}O_{11}$	*Streptomyces hygroscopicus* NRRL B-1865	188.5[d]	79	79
etheromycin (CP-38,295, C20-1, T50417)	[59149-05-2]	$C_{48}H_{82}O_{16}$	*Streptomyces* C20-12 FERM P-2736, *S. hygroscopicus* ATCC 31050	135–138	80,81	81,82
grisorixin (K358)	[31357-58-1]	$C_{40}H_{68}O_{10}$	*Streptomyces griseus*	75–80	83	84
epigrisorixin	[147384-59-6]	$C_{40}H_{68}O_{10}$	*S. hygroscopicus* NRRL B-1865		85	85

LL-C2320 delta	[107020-14-4]	$C_{47}H_{80}O_{15}$	*Streptomyces olivaceogriseus* NRRL 15357	164–168[d]	86	86
lonomycin A (DE3936, emericid, A218 SIPI-A4-0040)	[58785-63-0]	$C_{44}H_{76}O_{14}$	*Streptomyces ribosidificus* ATCC 31051, *S. hygroscopicus* FERM P-3159, *S. hygroscopicus* DS 24367	188–189[d]	87,89,91	88,90,92
lonomycin B	[68567-60-2]	$C_{44}H_{76}O_{14}$	*S. ribosidificus* ATCC 31051	181–182	93	94
lonomycin C	[68537-50-8]	$C_{44}H_{74}O_{14}$	*S. ribosidificus* ATCC 31051	186–187[d]	93	94
maduramicin alpha (LL-C23024, prinicin, X14868 A)	[79356-08-4]	$C_{47}H_{80}O_{17}$	*Actinomadura yumaense* NRRL 12515, *Nocardia* sp. X 14868 ATCC 31585	194–194[d]	95,96	69,96
maduramicin beta (X14868 C)	[79331-53-6]	$C_{46}H_{78}O_{17}$	*A. yumaense* NRRL 12515, *Nocardia* sp. X 14868 ATCC 31585	172–175[d]	95,96	69,96
martinomycin	[160791-16-2]	$C_{49}H_{84}O_{17}$	*Streptomyces salvialis* LL-D37187		97	97
27-methoxyseptamycin	[125131-53-5]	$C_{49}H_{84}O_{17}$	*Actinomadura* sp. ATCC 53676		98	98
mutalomycin (S11743 A)	[62618-08-0]	$C_{41}H_{70}O_{12}$	*Streptomyces mutabilis* NRRL 8088	163–171[d]	99	100
nigericin (K178, X464, polyetherin A, duamycin)	[28380-24-7]	$C_{40}H_{68}O_{11}$	*Streptomyces violaceniger* NRRL B1356, *S. hygroscopicus* E-749, 325-15	170–172	101,103,1-05	102,104
K41 A (A32887)	[53026-37-2]	$C_{48}H_{82}O_{18}$	*S. hygroscopicus* FERM P-1342, *Streptomyces albus* NRRL 11109	196–198[d]	106,108	107,109
K41 B	[72017-85-7]	$C_{54}H_{92}O_{20}$	*S. hygroscopicus* FERM P-1342	185–186[d]	110	111
CP-96,797	[14425-71-8]	$C_{47}H_{80}O_{17}$	*Streptomyces* sp. ATCC 55028		112	112
arenaric acid	[196202-51-4]	$C_{41}H_{68}O_{15}$	*Streptomyces* sp. CNH-248	106–108	113	113
semduramicin (UK61689)	[113378-31-7]	$C_{46}H_{76}O_{16}$	*A. roseorufa* ATCC 53666	167[d]	114	114
CP-120,509	[145174-89-6]	$C_{45}H_{76}O_{17}$	*A. roseorufa* ATCC 53666		115	115
septamycin (A28695 A, BL580 alpha)	[54927-63-8]	$C_{48}H_{82}O_{16}$	*S. hygroscopicus* NRRL 5678; NRRL 5647, *S. albus* NRRL 3883	164–166[d]	61,67,113	62,116,118
TMS582	[98791-39-0]	$C_{48}H_{68}O_{11}$	*S. hygroscopicus* TM 582	80–82	119	119
UK58852	[101621-29-8]	$C_{52}H_{88}O_{18}$	*A. roseorufa* ATCC 39697	123–126	73	73
W341 C	[110368-36-0]	$C_{47}H_{80}O_{16}$	*Streptomyces* W341 C		120	120
X146868 D	[79331-54-7]	$C_{47}H_{80}O_{17}$	*Nocardia* sp. X 14868 ATCC 31585	194–195	96	96
30 C, 2-Spiroketals						
A130 B	[73492-07-6][d]	$C_{54}H_{90}O_{16}$	*S. hygroscopicus* ATCC 21840		121	121

Table 1. (***Continued***)

Name[a]	CAS Registery number	Molecular formula	Producing organism	Mp, °C	Reference	
					I[b]	S[c]
A130 C	[73522-76-6]	$C_{47}H_{78}O_{13}$	*S. hygroscopicus* ATCC 21840		121	121
CP-53,607 (X14931 A)	[84680-56-8]	$C_{40}H_{66}O_{11}$	*Streptomyces halstedis* ATCC 31812, *Streptomyces* p. X 14931	199–204[d]	122,123	122,123
CP-80,219	[123286-64-6]	$C_{47}H_{78}O_{14}$	*S. hygroscopicus* ATCC 53626	176–180[d]	124	125
CP-82,483	[121962-58-1]	$C_{47}H_{78}O_{14}$			126	126
dianemycin	[38565-33-9]	$C_{47}H_{78}O_{14}$	*S. hygroscopicus* NRRL 3444	72–74	127	128
isodianemycin	[121962-58-1]	$C_{47}H_{78}O_{14}$	*S. hygroscopicus* NRRL 3444		126	126
eudusamycin (CP-63,517)	[100242041-9]	$C_{47}H_{78}O_{14}$	*S. endus* subsp. *aureus* ATCC 39574	95–105	129	129
19-epidianemycin (CP-60,993)	[93218-58-7]	$C_{47}H_{78}O_{14}$	*S. hygroscopicus* ATCC 39205	193–205[d]	130	130
lenoremycin (A130 A, Ro 21-6150)	[51257-84-2]	$C_{47}H_{78}O_{13}$	*S. hygroscopicus* X14563, ATCC 21840	87–92	131,133	132,134
leuseramycin (TM531 A)	[73537-10-7]	$C_{47}H_{78}O_{13}$	*S. hygroscopicus* ATCC 31590	88–91	135	135
moyukamycin	[96827-80-4]	$C_{47}H_{76}O_{13}$	*S. hygroscopicus* FERM BP-274		53,101,10-2,105,1-36,137	136
nanchangmycin	[65101-87-3]	$C_{47}H_{78}O_{14}$	*Streptomyces nanchangensis* NS 3226		138	138
TM531 B	[80118-77-0]	$C_{46}H_{76}O_{14}$	*S. hygroscopicus* ATCC 31590	251–253[d]	139	140
TM531 C	[80118-78-1]	$C_{46}H_{78}O_{15}$	*S. hygroscopicus* ATCC 31590	190–191	139	140
TM531 D	[87579-00-8]	$C_{46}H_{76}O_{14}$	*S. hygroscopicus* ATCC 31590		141	141
TM531 E	[87579-01-9]	$C_{46}H_{76}O_{14}$	*S. hygroscopicus* ATCC 31590		141	141
X14934A (CP-47,224)	[96998-05-9]	$C_{48}H_{80}O_5$	*Streptomyces* sp. X14934 NRRL 15518, *S. hygroscopicus* ATCC 31337	156–158[d]	142,143	142
30 C, Trispiroketal						
deoxy-epi-narasin	[70051-99-9]	$C_{43}H_{72}O_{10}$	*Streptomyces aureofaciens* NRRL 11181		144	144
deoxy-epi-salinomycin	[70022-35-4]	$C_{42}H_{70}O_{10}$	*Streptomyces albus* ATCC 21838	180	145	145
deoxynarasin	[70022-35-4]	$C_{43}H_{72}O_{10}$	*S. aureofaciens* NRRL 11181		144	144

deoxysalinomycin	[64003-50-5]	$C_{42}H_{70}O_{10}$	*S. albus* ATCC 21838		145	145
narasin A (A28086)	[55134-13-9]	$C_{43}H_{72}O_{11}$	*S. aureofaciens* NRRL 5758	98–100	146	147
narasin B	[58439-94-4]	$C_{43}H_{70}O_{11}$	*S. aureofaciens* NRRL 5758	150–153	148	148
narasin D	[58334-78-4]	$C_{44}H_{74}O_{11}$	*S. aureofaciens* NRRL 5758		148	148
salinomycin	[53003-10-4]	$C_{42}H_{70}O_{11}$	*S. albus* ATCC 21838	112–113	149	150
SY4 (5-hydroxysalinomycin)	[110947-74-5]	$C_{42}H_{70}O_{12}$	*S. albus* FERM P-419		151	151
SY8 (18,19-dihydrosalinomycin)	[111057-09-1]	$C_{42}H_{72}O_{12}$	*S. albus* FERM P-419		151	151
SY9 (20-oxosalinomycin)	[83564-04-9]	$C_{42}H_{68}O_{11}$	*S. albus* FERM P-419		152	152
31 C, 1-Spiroketal						
hidamycin (CP-51,532)	[84331-31-7]	$C_{42}H_{72}O_{13}$	*Actinomadura* sp. MI429-38F1; *Actinomadura verrucocopora* ATCC 31466	196–199[d]	153,154	153,155
31 C, Trispiroketal						
chloronoboritomycin A (X14766 A)	[75217-55-9]	$C_{43}H_{63}ClO_{14}$	*Streptomyces malachitofuscus downeyi* ATCC 31547	160	156	157
noboritomycin A	[68508-45-2]	$C_{43}H_{64}O_{14}$	*Streptomyces noboritoensis* NRRL 8123	235–237[d]	137	100
noboritomycin B	[68508-46-3]	$C_{44}H_{66}O_{14}$	*S. noboritoensis* NRRL 8123	220–222[d]	137	100
32 C, 0-Spiroketal						
ionomycin (EM94)	[56092-81-0]	$C_{41}H_{72}O_{9}$	*Streptomyces conglobatus* ATCC 31005	205–206[f]	158	159
32 C, Trispiroketal						
CP-44,161	[66771-51-5]	$C_{43}H_{66}O_{10}$	*Dactylosporangium salmoneum* ATCC 31222	155–157	160	161
34 C, 0-Spiroketal						
CP-73,064	[118674-05-8]	$C_{44}H_{76}O_{13}$	*Streptomyces* sp. ATCC 53523	214–216[d]	162	162
37 C, 0-Spiroketal						
alborixin (CP-38,986, S14750)	[57760-36-8]	$C_{48}H_{84}O_{14}$	*S. albus* 3840, *Streptomyces flaveolus* ATCC 31100	100–105	163,165	164
X206	[36505-48-3]	$C_{47}H_{82}O_{14}$	*Streptomyces* sp. X 206	133–145	27	166
Acyl tetronic acids						
A80577 (SF2487)	[123484-11-7]	$C_{42}H_{64}O_{12}$	*Actinomadura verrucospora* NRRL 18236, *Actinomadura* sp. FERM P-9063	250–252[d]	167,168	167,168

Table 1. (***Continued***)

Name[a]	CAS Registery number	Molecular formula	Producing organism	Mp, °C	Reference I[b]	Reference S[c]
tetronasin (ICI139603, M139603)	[75139-06-9]	$C_{35}H_{54}O_8$	*Streptomyces longisporoflavus* NCIB 11426	176–178[d]	169	170
tetronomycin	[82206-10-8]	$C_{34}H_{50}O_8$	*Streptomyces* sp. NRRL 11266	107–110[d]	171	171
Pyrrole ethers						
A23187 (calcimycin)	[52665-69-7]	$C_{29}H_{37}N_3O_6$	*Streptomyces chartreusis* NRRL 3882	181–182	172	173
A83094 (deethylkindanomycin)	[117615-33-5]	$C_{29}H_{39}NO_4$	*Streptomyces setonii*		174	174
AC7230	[108266-12-2]	$C_{28}H_{34}N_2O_7$	*Dactylosporangium* sp. AC7230	>300[d]	175	175
cafamycin	[112303-17-0]	$C_{30}H_{41}NO_4$	*Streptomyces* sp.	152–153	176	176
CP-61,405	[99623-84-4]	$C_{26}H_{30}N_2O_7$	*Streptomyces routienii* ATCC 39446	334–335	177	177
homoindanomycin	[129258-44-2]	$C_{32}H_{45}NO_4$	*Streptomyces galbus* NCAIM (P) 001036		178	178
indanomycin (X14547 A)	[66513-28-8]	$C_{31}H_{43}NO_4$	*Streptomyces antibioticus* NRRL 8167	138–141	179	180
X14885 A	[83917-57-1]	$C_{27}H_{32}N_2O_4$	*Streptomyces* sp. X 14885 NRRL 12350	264–266[d]	181	
Others						
BL580 zeta	[69522-23-2][d]		*S. hygroscopicus* NRRL 1108		70	[e]
UK44579	[83589-30-4][d]		*Actinomadura cremea* ATCC 31676		56	

[a]Alternative names are given in parentheses.
[b]References corresponding to isolations.
[c]References corresponding to structure determinations.
[d]Value given is for the sodium salt.
[e]Structure not yet determined.
[f]Value given is for the calcium salt.

Table 2. ***in vitro*** **Antimicrobial Activity of the Polyether Antibiotics**

	Minimum inhibitory concentration, μg/mL[a]a							
Polyether antibiotic	Staph. *aureus* ATCC No. 6538P	*Sarcina lutea* 9341	*Bacillus sp. E* 27859	*Bacillus subtilus* 558[b]b[c]c	*Bacillus megaterium* 8011	*Bacillus sp. TA* 27860	*Mycobacterium phlei* 355	*Streptomyces cellulosae* 3313
monensin	3.1	12.5	0.4	1.6	12.5	1.6	12.5	6.3
nigericin	0.2	0.1	0.004	0.1	0.1	0.02	0.4	0.4
grisorixin	0.4	0.2	0.1	0.2	0.1	0.4	0.2	0.2
salinomycin	3.1	3.1	0.2	0.8	0.2	0.8	6.3	3.1
narasin	0.8	1.6	0.2	0.9	0.4	0.4	3.1	3.1
lonomycin	1.6	12.5	1.6	3.1	0.8	1.6	12.5	6.3
X206	0.2	0.8	0.02	0.4	0.2	0.2	0.2	0.8
dianemycin	1.6	3.1	0.2	3.1	3.1	1.6	6.3	6.3
lenoremycin	0.2	0.2	0.02	0.4	0.1	0.4	0.2	1.6
septamycin	0.8	1.6	0.006	1.6	1.6	0.2	1.6	3.1
A204A	3.1	12.5	0.8	6.3	12.5	1.6	12.5	12.5
CP38952	12.5	6.3	1.6	6.3	3.1	3.1	3.1	12.5
lasalocid	1.6	3.1	0.2	1.6	3.1	1.6	12.5	6.3
isolasalocid	12.6	6.3	1.6	1.6	1.6	3.1	6.3	25
lysocellin	0.8	0.4	0.03	0.2	0.4	0.4	3.1	1.6
A23187	0.2	0.04	0.2	0.1	0.8	0.04	1.6	6.3
ionomycin		12.5	12.5	25	6.3			

[a]Lowest twofold dilution giving zone of inhibition in agar-well diffusion assay.
[b]NRRL collection number.
[c]Indicates no activity up to 50 μg/mL.

Table 3. **Ionophore Anticoccidial Agents Used for Prevention of Coccidiosis in Chickens (United States)**

Generic name	Trade name	Company	Year of first commercial use	Registered use level,g/t
maduramycin	Cygro	American cyanamid Co.	1985	5.0–6.0
monensin	Elancoban G200	ElancoProducts (division of Eli Lilly and Co.)	1971	99–120
	Monensin-100	C-Vet		
lasalocid	Avatec	Hoffman-La Roche	1977	75–125
narasin	Monteban	Elanco products (division of Eli Lilly and Co.)	1981	60–79
salinomycin	Bio-Cox	Agri-Bio (division of A. H. Robins)	1982	44–66
	Sacox 120	Hoechst		
	Salgain 60	C-Vet		