HHS Public Access

Author manuscript

Expert Opin Drug Discov. Author manuscript; available in PMC 2016 June 07.

Published in final edited form as:

Expert Opin Drug Discov. 2009 February ; 4(2): 109–146. doi:10.1517/17460440802661443.

Polyether ionophores: broad-spectrum and promising biologically active molecules for the control of drug-resistant bacteria and parasites

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Abstract

Background—As multidrug-resistant (MDR) pathogens continue to emerge, there is a substantial amount of pressure to identify new drug candidates. Carboxyl polyethers, also referred to as polyether antibiotics, are a unique class of compounds with outstanding potency against a variety of critical infectious disease targets including protozoa, bacteria and viruses. The characteristics of these molecules that are of key interest are their selectivity and high potency against several MDR etiological agents.

Objective—Although many studies have been published about carboxyl polyether antibiotics, there are no recent reviews of this class of drugs. The purpose of this review is to provide the reader with an overview of the spectrum of activity of polyether antibiotics, their mechanism of action, toxicity and potential as drug candidates to combat drug-resistant infectious diseases.

Conclusion—Polyether ionophores show a high degree of promise for the potential control of drug-resistant bacterial and parasitic infections. Despite the long history of use of this class of drugs, very limited medicinal chemistry and drug optimization studies have been reported, thus leaving the door open to these opportunities in the future. Scifinder and PubMed were the main search engines used to locate articles relevant to the topic presented in the present review. Keywords used in our search were specific names of each of the 88 compounds presented in the review as well as more general terms such as polyethers, ionophores, carboxylic polyethers and polyether antibiotics.

Keywords

antibacterial; antibiotics; antifungal; antimalarial; antiviral; carboxylic polyether; drug resistance; ionophore; polyethers

1. Introduction

Polyether antibiotics or carboxyl ionophores [1,2] represent a unique class of compounds reported as potent antibiotics that belong to the larger family of naturally occurring

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ionophores. First used in 1967, the term ionophore refers to the molecule's ability to bind a metal ion and facilitate its transport across cellular membranes. This chemo-physiological property has made polyether ionophores a useful tool in the study of cation transport mechanisms and has been the rationalization for their biological activities [1,3].

Polyether antibiotics are believed to affect their targeted cells by means of the modification of the permeability of cellular membranes to cationic metal species. Polyether ionophores possess distinctive structural features that are crucial to their ability to interact with metal species. These features include an exterior alkyl backbone that confers their lipophilic characteristics and an oxygen-rich internal cavity that can bind metal ions [2,4,5].

Naturally occurring ionophores are grouped into three categories with regard to the mechanism through which membrane permeability is altered. The first group is the mobile carriers that bind the metal species in an internal polar cavity thus shielding their charge. The second group is the quasi-ionophores. These molecules form *trans*-membrane hydrophilic channels through which metal ions flow through the membrane. The last group consists of the neutral ionophores that facilitate the diffusion of cations across membranes according to the membrane potential [2,7].

Naturally occurring carboxyl ionophores are relatively high in molecular weight, 500 – 1,000 amu, and are lipid-soluble compounds that display a high affinity for cations such as K^+, Na^+, Ca^{2+}, thus yielding mobile cation complexes that can freely travel across biological membranes [1]. Their affinity for specific metal ions differs by the electrostatic neutralization of the cation and by the position of the charged carboxylate and its ability to form an ionic or quasi-ionic bond with a cation. With the exception of lasalocid (**1**), all naturally occurring carboxyl ionophores possess an affinity for Na^+ and K^+. Lasalocid (**1**) forms dimers and divalent complexes with Ca^{2+} and Mg^{2+}. This metal complex formation results in a paracyclic complex as a result of the head-to-tail hydrogen bonding.

The normal physiologic steady state of most living cells is dependent on the establishment of intracellular and extracellular concentration gradients of Na^+ and K^+. Intracellular concentrations of K^+ are higher than that of Na^+ and extracellular concentrations are respectively reversed [6]. These ion concentration gradients are essential for cell function. Carboxyl ionophores can easily penetrate cellular membranes owing to their lipophilic properties [6,8,17] and perturb the intracellular cation balance.

Owing to the intrinsic necessity of establishing *trans*-membrane electrical potentials for cell metabolism by means of the establishment of ion gradients, carboxyl ionophores present significant biological interest not only for their therapeutic utility but also for the possibility of using these chemo-physiological dynamics in combination with traditional or current therapeutics [3,8,9].

A total of 53 bacteria of *Streptomycetaceae* family are reported to produce carboxyl ionophores. These microorganisms belong to three genera, *Streptomyces, Actinomadura* and *Dactylosporangium. Streptomyces* sp are the main producers of these types of compounds and ~ 50% of the carboxyl ionophores known at present are derived from two *Streptomyces* species (*Streptomyces hygrocropicus* and *Streptomyces albus*) [1]. Industrially, these highly

biologically active molecules are produced by several microorganisms at low cost and in a predictable manner; thus their industrial production is well established via industrial fermentation and represents an asset in replacing or augmenting existing therapies owing to the establishment of resistance [3,10,11].

2. Biological activity

Polyether antibiotics show a broad spectrum of bioactivity including antibacterial, antifungal, antiparasitic, antiviral and tumor cell cytotoxicity. In addition to the previously mentioned biological activities, several studies have investigated the potential herbicidal [12] and anti-inflammatory activities [13] of these highly active molecules as well as their effects on the CNS and immunoregulatory systems (Table 1) [14,15].

2.1 Antibacterial

The antibacterial potential of carboxyl ionophores is widely documented with reports on the discovery of these compounds typically mentioning their activity against Gram-positive and Gram-negative bacteria, as well as some fungi. From these reports it can easily be gathered that carboxyl polyethers are molecules of outstanding potency against numerous pathogenic bacteria (drug-sensitive and drug-resistant). The fact that their potency against serious threats such as Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) rivals that of clinically used drugs such as vancomycin and oxacillin adds to their potential utility. At this point it is difficult to fully assess the true value of these molecules as potential therapeutic agents simply because, on the basis of the reports gathered here, none of these molecules have been assayed in an animal model infected with these bacteria. Thus at this stage all that can be summarized from the reports presented later is that carboxyl polyethers are selective and potent antibacterial agents *in vitro*. They are appealing as antibacterial agents because of their ability to inhibit growth of MRSA and VRE at very low concentrations, both of which are major public health threats.

2.1.1 Activities against drug-sensitive bacteria strains—A similar inhibitory pattern emerged from reports on the antibacterial potential of carboxyl polyethers with respect to a strong selectivity towards Gram-positive bacteria [1,5,10,8,16,17–19,20,21]. Monensin (**2**), narasin (**3**), salinomycin (**4**), nigericin (**5**), lenoremycin (**6**), septamycin (**7**), carriomycin (**8**), X-14766A (**9**), noboritomycin A (**10**), alborixin (**11**), ionomycin (**12**), A23187 (**13**), X-14547A (**14**), lysocellin (**15**) and lasalocid (**1**) were all evaluated against eight Gram-positive bacteria (cocci, rods, filamentous) as well as against seven Gram-negative bacteria, and four fungal species. All but ionomycin (**12**) showed potent activity against Gram-positive bacteria (MIC varying in the range 0.006 – 12.5 μg/ml). In contrast, not one of these compounds displayed activity against the tested Gram-negative bacteria (MIC > 100 μg/ml). Several other carboxyl ionophores are reported as having a similar biological activity profile against Gram-negative, and Gram-positive bacteria. These are grisorixin (**16**) [11], lonomycin (**17**) [18], octacyclomycin (**18**) [19], X-14931A (**19**) [16], dianemycin (**20**) [8], lonomycin B (**21**) [10] and C (**22**) [10], antibiotic 6016 (**23**) [20], inostamycin (**24**) [22], inostamycin B (**25**) [22] and leuseramycin (**26**) [23].

Not all carboxyl polyethers show this selectivity towards Gram-positive bacteria. Compounds such as septamycin (**7**), noboritomycin A (**10**) and B (**27**) stand out for their ability to target not only Gram-positive bacteria but also Gram-negative bacteria. The reported MIC of septamycin (**7**) against *Escherichia coli* was 0.1 μg/ml [24]. Noboritomycin A (**10**) and B (**27**) inhibited the growth of *Neisseria pharyngi* with an MIC of 0.01 μg/ml [25]. The MIC of mutalomycin (**28**) against the same pathogen was 0.3 μg/ml [26].

Not all carboxyl ionophores possess significant activity against Gram-positive bacteria. For example, laidlomycin (**29**) was reported as inactive against *Staphylococcus aureus* [27].

Although in general anaerobic bacteria are more resistant to carboxyl polyethers, few *Clostridium* sp, *Eubacterium* sp, *Propionibacterium* sp and *Peptococcus* sp are reported extremely sensitive to compounds such as nigericin (**5**), monensin (**2**), dianemycin (**20**), lysocellin (**15**), lasalocid A (**1**) and A23187 (**13**) with MIC values as low as 0.049 μg/ml in many cases [1].

Carboxyl ionophores have broad-spectrum activity against Gram-positive but not Gram-negative bacteria. Guyot *et al.* [28] attributed this overall differential selectivity to the presence of an outer membrane in Gram-negative bacteria. The outer membrane is believed to be impermeable to hydrophobic compounds. These authors came to this conclusion while using autoradiography; they could show that only *Bacillus cereus*, not *E. coli*, could incorporate the radiolabeled calcimycin (**13**) [29].

2.1.2 Activities against multidrug-resistant strains of bacteria—Carboxyl polyethers were reported as potent agents against a variety of multidrug-resistant (MDR) strains of pathogenic bacteria. Lycocellin (**15**), for instance, was reported as active against a streptomycin-, erythromycin-, chloramphenicol- and penicillin-resistant strain of *S. aureus*, MIC 4 μg/ml [17]. The MIC for the Na^+ salt of the antibiotic No 6016 (**23**) against a similar strain was reported to be 1.56 μg/ml [20]. Noboritomycin A (**10**) and B (**27**) are also reported as being active against several resistant strains: penicillin-resistance strains of *S. aureus*, MIC 0.01 μg/ml, tetracycline-resistance strains of *Micrococcus* sp, MIC 0.01 μg/ml, aminoglycoside-resistant strains of *Streptococcus faecalis*, MIC 0.01 μg/ml and macrolide-resistant strains of *Sarcina lutea*, MIC 0.01 μg/ml [25]. Septamycin (**7**) (Na^+ salt) was also reported effective against these same strains: penicillin-resistant strain of *S. aureus*, MIC 0.31 μg/ml, tetracycline-resistant strain of *Micrococcus* sp, MIC 0.31 μg/ml, aminoglycoside-resistant strain of *Streptococcus faecalis*, MIC 0.1 μg/ml and macrolide-resistant strain of *Sarcina lutea*, MIC 0.31 μg/ml [24].

In 2007, Yoo *et al.* [30] published a report on the potential of several carboxylic polyethers, laidomycin (**29**), monensin (**2**), salinomycin (**4**) and narasin (**3**), to inhibit two resistant bacterial strains, VRE and MRSA [30]. The MIC of all tested carboxyl ionophores against MRSA and VRE varied from 0.5 to 4 μg/ml and from 8 to 16 μg/ml, respectively, narasin being the most potent in both cases. These compounds were more potent than vancomycin and oxacillin. The MIC of vancomycin against VRE was 64 μg/ml and that of oxacillin against MRSA was > 32 μg/ml [30].

2.2 Antifungal

In general, fungi are more resistant to carboxyl ionophores. In several reports, MIC values were greater than the highest tested concentration [1,11,17–19].

There are some exceptions: several species of fungi such as *Paecilomyces variotii, Candida albicans, Saccharomyces cerevisiae* and *Penicillium digitatum* are reported as moderately sensitive to some carboxylic polyethers, for example, grisorixin (**16**) [11], monensin (**2**) [1], narasin (**3**) [1], salinomycin (**4**) [1], lenoremycin (**6**) [1], carriomycin (**8**) [1], alborixin (**11**) [1], A23187 (**13**) [1], dianemycin (**20**) [11], lysocellin (**45**) [1], X-14931A (**48**) [16] and leuseramycin (**26**) [23], with MIC values varying in the range of 20 – 100 μg/ml. *P. variotii, C. albicans, S. cerevisiae* and *P. digitatum* were quite sensitive to several other carboxyl polyethers such as lysocellin (**15**) [1], A23187 (**13**) [1], lenoremycin (**6**) [1] and nigericin (**5**) [1]. The MIC values for these compounds were < 2 μg/ml.

More recent studies about the antifungal capacities of carboxyl ionophores focused on opportunistic infections of *Pneumocystis carinii* [31,32]. HIV patients who develop AIDS have a particular need for a new, effective and prophylactic therapy to pneumocytosis. Lasalocid (**1**) and nigericin (**5**) (Figure 1), two common carboxyl ionophores, were shown to have a significant inhibitory effect on the growth of *P. carinii in vitro*. Lasalocid (**1**) at 0.05 μg/ml induced a 91.3 and 92.0% reduction in cyst and trophozoite concentrations, respectively. Nigericin (**5**) at a concentration of 0.05 μg/ml was 100% effective in reducing both morphologies of the fungi, although cytolytic effects on the cells monolayer were observed [31]. Lasalocid (**1**) was tested *in vivo* and showed promising activity in prophylactic use including the ability to prevent the occurrence of pneumonitis in corticosteroid-immunosuppressed Sprague–Dawley rats in a dose-dependent manner. The dosage of lasalocid (**1**) 10 mg/kg/day was protective for 80% of infected rats whereas the dose of 20 mg/kg/day was reported to be safe and nontoxic. All rats from this group were protected from the disease [32].

2.3 Antiparasitic

2.3.1 Plasmodium sp—The emergence and spread of resistant strains of the malarial parasites to several of the antimalarial drugs marketed at present, specifically chloroquine, constitute a serious public health threat in countries all around the world, most of which are poor [33–36]. To address the emerging resistant strains, the simultaneous use of more than one drug known to have different mechanisms of action (MOAs) is considered an important change in the approach to fighting malaria. Such an approach slows the development of resistance to an individual drug, thus limiting the spread of resistant strains [37]. The success of combination therapy is dependent on the availability of molecules with unique MOA. In recent years, a great deal of effort has been dedicated to the discovery of new antimalarial agents. Among the potential candidates reported thus far are carboxyl ionophores. From the reports we gathered, it emerges that these molecules stand out as potential antimalarial drug candidates for several reasons.

First, carboxyl ionophores are reported as potent *in vitro* antimalarial agents, with IC_{50} values in the nanomolar and picomolar range [38,39]. Carboxyl ionophores are typically

organized into three subclasses. The first category includes compounds specific to monovalent cations such as alborixin (**11**), lonomycin A (**17**), nigericin (**5**), grisorixin (**16**), narasin A (**3**), salinomycin (**4**), cationomycin (**31**) and monensin A (**2**) (Figure 1). The second includes molecules specific to divalent cations such as calcimycin (**13**), X14885 A (**30**), X14547A (**14**) (Figure 1). The third includes molecules that show less specificity towards monovalent or divalent cations, that is, lycocellin (**15**), lasalocid A (**1**) and ionomycin (**12**). Of these three subgroups, carboxyl ionophores specific to mono valent cations are reported as the most potent, apart from cationomycin (**31**) having IC_{50} = 35 μg/ml, with IC_{50} values in the range of 0.6 – 6.5 μg/ml (Alborixin, IC_{50} = 0.6 μg/ml; lonomycin, IC_{50} = 1.4 μg/ml; nigericin, IC_{50} = 1 μg/ml; grisorixin, IC_{50} = 0.9 μg/ml; narasin A, IC_{50} = 1 μg/ml; salinomycin, IC_{50} = 2.8 μg/ml) [38,39].

Second, carboxyl ionophores are also reported to have potent activity *in vivo*. Gumilla *et al.* [40] evaluated the *in vivo* antimalarial potential of alborixin (**11**), lonomycin A (**17**), nigericin (**5**), narasin (**3**) and monensin A (**2**) using rats infected with *Plasmodium chabaudi* and *Plasmodium vinckei petteri* [40]. Alborixin (**11**), lonomycin A (**17**), nigericin (**5**), narasin (**3**) and monensin A (**2**) showed significant *in vivo* antimalarial activity: decreasing the parasitemia by ≥70% by day 5 in *P. chabaudi* and *P vinckei petteri* infected mice. Overall, the ED_{50} varied between 0.4 and 4.1 mg/kg. Carboxyl ionophores that are specific to monovalent ions including alborixin (**11**), lonomycin A (**17**), nigericin (**5**), narasin (**3**) and monensin A (**2**) seemed to be the most potent of all the three subclasses *in vivo* as was the case *in vitro*. The therapeutic index using the intraperitoneal route of administration for lonomycin A (**17**), nigericin (**5**), narasin A (**3**), monensin A (**2**) and lasalocid A (**1**) ranged from 2 to 6 [40]. Adovelande and Schrevel also assessed the *in vivo* antimalarial activity of monensin (**2**) and nigericin (**5**) using *P. vincke petteri* infected mice. The ED_{50} and ED_{90} values for monensin (**2**) were 1.1 and 3.5 mg/kg, respectively. The ED_{50} and ED_{90} for nigericin (**5**) were 1.8 and 4.6 mg/kg, respectively. Monensin (**2**) seemed more effective at curing mice than nigericin (**5**); 100% of mice that received 10 mg/kg of monensin (**2**) were cured whereas only one-third of mice that received this dose of nigericin (**5**) were cured [41].

Third, several studies reported that these compounds could act in a selective manner and that the level of toxicity varied from one subclass of carboxyl ionophores to another. Gumila *et al.* [42] reported the *in vitro* differential ionophore activity between *Plasmodium falciparum* and normal mammalians cells, Human Jurkat lymphoblasts and U937 macrophage cell lines. It seemed that mammalian cells were only affected by compounds such as nigericin (**5**), alborixin (**11**), lonomycin (**17**), narasin (**3**) and monensin (**2**) at concentrations that are significantly, at least 35-fold, higher than the IC_{50} against the malarial parasite [38]. Whereas the IC_{50} of narasin (**3**), monensin (**2**) and nigericin (**5**) against the malarial parasite varied in the range 0.6 – 1.0 μg/ml, their MV_{50} against U937 macrophage varied between 23.5 and 305 μg/ml and their LV_{50}, LD_{50} against Jurkat lymphoblast, between 45 and 500 μg/ml [38]. These authors also reported on the *in vivo* toxicity that seemed to be dependent on the subclass of the molecule, that is, its specificity towards monovalent or divalent cation species. Gumilla *et al.* [40] assessed the acute and subacute toxicity of alborixin (**11**), lonomycin A (**17**), nigericin (**5**), narasin (**3**) and monensin A (**2**) using rats infected with *P.*

chabaudi and *P. vinckei petteri* [40]. Alborixin displayed the highest acute toxicity, LD_{50} = 1 mg/kg, after intraperitoneal administration. Overall, carboxyl ionophores that are specific monovalent-ion complexing, that is, alborixin (**11**), lonomycin (**17**), nigericin (**5**), narasin (**3**) and monensin A (**2**), seemed to be more toxic with LD_{50} values between 4 and 30 mg/kg. The LD_{50} values for polyethers specific to divalent metal ions on the other hand varied in the range of 30 – 80 mg/kg [40]. In similar findings, Berger *et al.* [43] found the acute toxicity of lasalocid A (**1**) and nigericin (**5**) to be 2.5 and 40 mg/kg, respectively.

Fourth, two carboxyl ionophores were reported to be significantly more potent than chloroquine. Adovelande and Schrevel assessed the antimalarial activity of monensin (**2**) and nigericin (**5**) alongside chloroquine and showed that *in vitro* these were, respectively, 25- and 30,000-fold more potent [41].

Fifth, several carboxyl ionophores were reported as having outstanding activity against chloroquine-resistant strains. Otoguro *et al.* [44,39] published two reports in 2001 and 2002 in which the effects of several carboxyl ionophores were evaluated against chloroquine-resistant and sensitive strains of *P. falciparum* alongside several drugs marketed at present. These antimalarial agents were artesumate, artemisin, chloroquine, pyrimethamanine, amodiaquine and quinine trimethamine trimethoprim [44,39]. These studies revealed that carboxyl ionophores such as X-206 (**32**), lonomycin A (**17**), nigericin (**5**), narasin (**3**), salinomycin (**4**), dianemycin (**20**), monensin (**2**) and lysocellin (**15**) were extremely potent against chloroquine-resistant strains of *P. falciparum* with IC_{50} values varying in the range 0.15 – 6.4 nM. These molecules seemed to be more potent than the standard drugs mentioned earlier. The IC_{50} values for these drugs varied from 7.6 to values > 100,000 nM. Artemether (IC_{50} = 7.6 μg/ml) was the most potent of these compounds. The cytotoxicity against mammalian cells, human diploid embryonic cell, was also assessed. In this study several ionophores, lasalocid A (**1**), octocyclomycin (**18**) and X-206 (**32**) displayed high selectivity indexes. The highest selective index was that of X-206 (**32**), that is, 3,673 against chloroquine-resistant strain and 1,080 against chloroquine-sensitive strain. These compounds showed higher potency and selectivity towards chloroquine-resistant strains when compared to chloroquine-sensitive strain [39]. Last, the authors performed a comparative assessment of the *in vivo* effect of X-206 (**32**), artesunate and artemether in *Plasmodium berghei* infected mice. X-206 (**32**) showed a narrow therapeutic window and had an ED_{50} = 0.53 mg/kg, the lowest evaluated. It was found to be toxic when > 3 mg/kg. Berger *et al.* [43] estimated the acute toxicity of X-206 (**32**) to be 11 mg/kg. In 2002, these authors reported another compound, K-41 (**33**), active *in vitro* against a chloroquine-resistant strain of *P. falciparum*. K-41 (**33**) (IC_{50} = 8.5 nM) showed activity similar to that of artemether and artesunate and was more potent than artemisinin, chloroquine and pyrimethamine. K-41 (**33**) had a moderate selectivity index *in vivo*; it was active orally against chloroquine-resistant strains, the ED_{50} (7.0 mg/kg) was close to that of artemether, chloroquine and artesunate. As far as acute toxicity of K-41 (**33**) is concerned an LD_{50} > 100 mg/kg was reported [44].

Finally, carboxyl ionophores affect the malaria parasite by means of a mechanism that is distinct from that of drugs available at present. Although there is some conjecture over this subject, some authors believe this MOA could be similar to that of chloroquine and others

believe it is completely different [38,40,41]. It is generally accepted that carboxyl ionophores act via anti-transport of cation with H^+ after inserting themselves in cellular membranes [2]. Adovelande and Schrevel believe that this could result in the alkalination of the food vacuole of the parasite in a similar manner as chloroquine [41]. Chloroquine is reported to act in two ways: by increasing the internal pH of the food vacuole and by binding to ferriprotoporphyrin thus preventing its crystallization into hemozoin. This will then accumulate to a toxic level inside the vacuole [41,45,46]. The mechanism proposed by Gumilla *et al.* [38] is different from that of chloroquine [38]. According to these authors, the anti-transport of cations with H^+ cannot justify the outstanding potency of these compounds, for the simple reason that changes that occur in the plasma membrane of infected erythrocytes reduce the efficiency of ion shuttling across the membrane. These authors believe that carboxyl ionophores do not merely insert themselves in plasma membrane but are completely internalized [38,47]. Once inside the cell and in close proximity with the parasite, they can inhibit its development either by altering its ion content or by disturbing the preestablished ionic gradient between the host and parasite cytosol [38]. The parasite is reportedly more sensitive during the shizont stage [40].

A polyether isolated from the marine *Streptomyces* sp. H-668 and named hawaiimycin-I (**34**) (Figure 1) [48] reinforced the critical role of certain key structural features including the terminal carboxylic group on the bioactivity of carboxyl ionophores. Hawaiimycin-I (**34**) is extremely close structurally to a set of carboxyl ionophores reported as potent antimalarial [40,44], that is, monensin A (**1**), K-41 (**33**), nigericin (**5**), lonomycin (**17**) and grisorixin (**16**). These molecules share a unique skeleton:5 interconnected furan and pyran rings. The key difference with hawaiimycin-I (**34**), established to have only a weak antimalarial activity (IC_{50} = 100 – 200 ng/ml against *P. falciparum*) [48], is the absence of the terminal carboxylic group. Crystal structures of this type of compounds reveal that the terminal carboxylic moieties can either be implicated in ion coordination or be involved in hydrogen bonding with distant OH groups [2,5].

Toxicity concerns remain the primary hindrance in the development of carboxyl polyethers into antimalarial drugs. Apart from this issue, it can be gathered from the literature that carboxyl polyethers possess a great potential as antimalarial drug candidates and leads for further optimization. Carboxyl polyethers owe their outstanding potency, *in vitro* and *in vivo*, to their unique MOA. Studies published by Gumilla *et al.* [40] illustrate that it is possible through semisynthetic modification of these molecules to generate more desirable drug candidates. These authors reported that the therapeutic index could be improved in the case of monensin and lasalocid A; the therapeutic index of monensin A (**2**) is 5 p.o. but that of its synthetic analogue, monensin A (**2**) methyl ether, is 12 i.p. The therapeutic index of lasalocid A (**1**) is 3.3 i.p. but that of its analogue, 5-bromo lasalocid A (**1**), is 22 i.p. [40].

2.3.2 Eimeria sp—*Eimeria* sp are apicomplexan protozoan parasites and etiological agents of coccidiosis, a disease affecting cattle and poultry. In an attempt to control these diseases, anticoccidial drugs are generally added to the feed of these animals. Several carboxylic polyethers are among the drugs that are now approved for use as control therapeutics for coccidiosis. The first approved application of veterinary carboxyl ionophores was in the prophylactic and therapeutic treatment of coccidiosis in poultry [49,50,51]. Carboxylic

ionophores are reported to also have a positive impact on the growth of these animals [52,53]. Maduramicin (**35**), salinomycin (**4**), narasin (**3**), lasalocid (**1**) and monensin (**2**) are the most prevalent of the feed additives marketed at present [1,52,53,54]. Several other carboxyl ionophores are also reported to have anticoccidial utility in chickens and turkeys. Although these are the most common additives used now, there are several other carboxyl ionophores reported to be more effective than additives marketed at present [49–59].

Dirlam *et al.* [57] performed a comparative study of the anticoccidial activity of CP-82,009 (**36**), salinomycin (**4**) and maduramicin (**35**) in chickens infected with several pathogenic strains of *Eimeria: Eimeria tenella, Eimeria necatrix, Eimeria acervulina, Eimeria maxima* and *Eimeria brunette*. CP-82,009 (**36**) at doses of 5 or 10 mg/kg of feed showed a broader spectrum and tolerance [57]. These same authors reported in 1990 that another carboxyl polyether, CP-84,657 (**37**) had outstanding anticoccidial potential. This agent at a dosage ≤5 mg/kg cured chickens infected with different types of *Eimeria* sp. CP-84,657 (**37**) was more potent than several molecules, such as salinomycin (**4**), narasin (**3**), lasalocid (**1**) and monensin (**2**), marketed at present [54]. CP-80,219 (**38**) was reported to have anticoccidial effects against *E. tenella* in chickens at dosages of 30 and 120 mg/kg of feed [55].

Kijimicin (**39**), tested along with monensin (**2**) and salinomycin (**4**) in chicken infected with *E. tenella*, was more effective than several marketed drugs. Its anticoccidial index (ACI) was 156.8 versus 144.1 for monensin (**2**) sodium salt and 127.1 for salinomycin (**4**) sodium salt [56].

Endusamycin (**40**) showed a protective effect on chicken infected with *E. tenella* and *E. acervulina* at doses of 10 – 40 mg/kg of feed [58]. The toxicity of this compound in rats was analyzed; when administered to rats orally, the LD_{50} was 7.5 mg/kg orally [58].

Liu *et al.* [59] reported that X-14868A (**41**) and X-14868B (**42**) were potent anticoccidial agents for chickens infected with *E. tenella*. Doses of 7 and 15 mg/kg of X-14868A (**41**) and X-14868B (**42**), respectively, were estimated to be protective quantities against coccidiosis. These agents are more potent than well-known coccidiostats agents. For example, monensin (**2**) required doses are 98 – 121 mg/kg, lasalocid (**1**) required doses are 75 – 125 mg/kg and salinomycin (**4**) doses are 60 – 100 mg/kg [59].

Smith and Strout suggested an MOA for the coccidiocidal effect of carboxyl ionophores [51]. They suggested that anticoccidial agents act either by inhibiting the development of intracellular parasites or by inducing destruction of intracellular sporoizoids [51].

2.3.3 Cryptosporidium parvum—*Cryptosporidium parvum* infections in immunocompetent individuals are generally self-limiting. In immunocompromised patients, particularly in AIDS patients, these infections are severe and are becoming increasingly prevalent [60–62]. Although many drugs are used for the clinical treatment of *C. parvum*, the effective treatments of infected AIDS patients are limited [60,61]. The screening of several anticoccidial molecules has led to the *in vitro* and *in vivo* examination of several carboxyl ionophores [63,64–68]. Monensin (**2**), maduramicin (**35**), salinomycin (**4**), alborixin (**11**) and lasalocid (**1**) were all evaluated for their respective activity against *C.*

parvum [63,64–66,69,70]. When compared with control anticoccidial agents, monensin (**2**) reduced the development of *C. parvum* by > 90% [65]. Treatment with maduramicin (**35**) and alborixin (**11**) of severe combined immune deficient (SCID) mice inoculated with 10^6 oocysts (bovine) oral gavage, beginning 4 weeks post infection at 3 mg/kg/day for 3 weeks, resulted in a 96% reduction in fecal parasite load ($p < 0.003$) with maduramicin (**16**) [69]; this correlated with significant reductions in parasite loads in cross-sections of small intestine tissue ($p < 0.000002$) and colon ($p < 0.000006$). Alborixin (**12**) showed less effective results with oocyst reduction at 71% after 3 weeks [69]. Although some toxicity was observed, illustrated by some weight loss, the significant anticryptosporidial activity was overwhelming over this moderate toxicity [69].

2.3.4 Toxoplasma gondii—A parasite that infects a wide variety of organisms, *T. gondii* is best known for its neurological effects and its particularly hearty cystic stage [71–74]. *T. gondii's* most deleterious activity is its induction of toxoplasmic encephalitis, thus causing fatal CNS lesions. This is an especially opportunistic pathogen in AIDS patients [73–77]. Treatment for toxoplasmic encephalitis is typically a combination therapy of pyrimethamine and sulfadiazine. Unfortunately, this type of chemotherapy is not effective against the cystic stage of *T. gondii*, thus reactivation of the bradyzoites is chronic, especially in the CNS [14,78]. Previous data has demonstrated that several polyether antibiotics are highly active against the tachyzoite stage of *T. gondii* [74,76,79–81]. A double *in vitro* and *in vivo* study on the bradyzoites stage revealed under immunofluoresence and electron microscopy that very low dosages, 0.0001 μg/ml, of monensin (**2**) significantly altered the cytological physiology, that is, swollen cysts and large numbers of vacuoles, of *T. gondii* [76]. Temporal, *in vivo* mouse brain *T. gondii* bradyzoites, evaluations of a 6- and 48-h exposure yielded significant antiparasitic activity [57,82]. Six-hour single dose treatment of 0.1 μg/ml of monensin (**2**) effectively eliminated the viability or lysed the cells completely. In a similar 48-h trial with concentrations of as little as 0.0001 μg/ml, the bradyzoites were swollen or lysed, and at a concentration of 0.01 μg/ml all parasites seemed permanently altered beyond viability under electron microscopic evaluation [76]. Apart from carboxyl ionophores antibiotics only two other drugs have shown activity against the bradyzoites stage, atovaquone [83] and 2′–3′-dideoxyinosine (ddi) [84]. *In vitro* and *in vivo* tests have shown that these other molecules take a significantly longer time to have the same activity as monensin (**2**) [57,74,81,82,]. Monensin (**2**) is lethal to cystic forms of *T. gondii*, which is rapid and independent of the metabolic activity of the bradyzoites [83].

2.3.5 Neospora canium—The coccidian parasite *N. canium* is often misdiagnosed as *T. gondii*. Owing to its recent discovery, few evaluations of antiparasitic therapeutics have been evaluated, although of these few evaluations, predictable results of the antimicrobial effects of naturally occurring carboxyl polyethers were illustrated [85]. To examine the inhibition of tachyzoite multiplication, a 2-day treatment monoclonal antibody-based enzyme immunoassay (EIA), and a 5-day cell culture flask (CCF) treatment and a lesion-based assay were developed. In this study, 43 chemotherapeutics, sulfonamides, dihydrofolate reductase/thymidylate synthase inhibitors, macrolides, lincosamides, pentamidine analogues, eight miscellaneous antiprotozoal and six carboxyl polyethers were evaluated for use in treating *Neospora canium* infections. This assay determined that five out of the six ionophores

evaluated, that is, lasalocid (**1**), maduramicin (**35**), narasin (**3**), monensin (**2**) and salinomycin (**4**), caused 100% reduction in tachyzoite induced lesions at concentrations of 0.000001 μg/ml in the CCF assay, which was the lowest concentration examined. Alborixin (**11**) was toxic to host cells at these concentrations [85].

2.4 Antiviral activity

From the literature reviewed, it can be gathered that carboxyl polyethers possess several features that could qualify them as promising anti-HIV-1 leads. Although none of the reports reviewed assessed the potency of these molecules alongside clinically used drugs the reported IC_{50} values against HIV-1 targets are, however, significant. These molecules are also reported to have the potential to inhibit the replication of the virus in key cells such as CD4-expressing lymphoid cells and mononuclear phagocytes. In addition, carboxyl polyethers have proven to be effective against acute as well as chronic infections *in vitro*. The effective dose and toxicity level varied from molecule to molecule but few molecules have proven effective at nontoxic concentrations. As a group, carboxyl polyethers do not belong to any of the class of anti-HIV drugs known at present. Some carboxyl polyethers such as monensin (**2**) and kijimicin (**39**) were evaluated as protease inhibitors, with respect to their interference with posttranslational modifications of HIV-1 proteins. It is well established that HIV-1, which has an extremely high mutation rate, easily develops resistance to protease inhibitors by altering the active site of the targeted protease enzyme. Whether carboxyl polyethers that interfere with posttranslational modifications of HIV-1 proteins will share this fate is not well established at this time owing to the limited understanding of the exact sequence of events through which compounds such as monensin (**2**) and kijimicin (**39**) impair posttranslational modification. None of the studies reviewed investigated the effectiveness of these carboxyl polyethers in an animal model.

2.4.1 Activity against HIV-I-AIDS—Several reports describe the potential of carboxyl ionophores, monensin (**2**), salinomycin (**4**), lasalocid (**1**), nigericin (**5**), dianemycin (**20**), alborixin (**11**), kijimicin (**39**), SF2361 (**43**), SF2324 (**44**), SF2487 (**45**) and laidomycin (**29**) as anti-HIV agents [86_91].

Nakamura *et al.* [88] assessed the effect of 10 carboxyl ionophores, monensin (**2**), salinomycin (**4**), lasalocid (**1**), nigericin (**5**), dianemycin (**20**), alborixin (**11**), kijimicin (**39**), SF2361 (**43**), SF2324 (**44**) and SF2487 (**45**), on the replication of HIV-1. All but SF2324 (**44**) showed a dose-dependent inhibition of the virus replication. Apart from SF2324 (**44**), the concentration that inhibited reverse transcription activity, viral replication, by 50%, EC_{50}, varied in the range 0.40 ± 0.040 to 7.12 ± 4.4 μg/ml. The IC_{50} concentration that decreases cell viability by 50% of SF2324 as its EC_{50} in H9 cells, primary infection, was determined to be > 100 μg/ml, the highest tested concentration. The IC_{50} of the remaining compounds varied in the range 6.98 ± 2.9 to 78 ± 4.7 μg/ml (Table 2). For these compounds an inhibitory effect at nontoxic dose was observed. The ratio IC_{50}/EC_{50} varied in the range 3.18 – 76.72 μg/ml (Table 2). The chronically infected cells, U937, were sensitive to all but SF2487, but a higher cytotoxicity was observed as shown by the low IC_{50}/EC_{50} ratio, which varied here from 1.18 to 8.32 μg/ml (Table 2) [86,88].

It is believed that all carboxyl ionophores do not share a common MOA against HIV. These compounds target different stages of the HIV infective cycle, that is, the pre- and post-absorption steps [86–90]. Nakamura *et al.* [88], using a time of addition design, exposure of H9 cells to these molecules before, during and after viral absorption, partitioned these agents in two main groups on the basis of their MOA. The first group, believed to inhibit viral absorption was made of lasalocid (**1**), dianemycin (**20**), SF2361 (**43**), SF2324 (**44**), SF2487 (**45**) and alborixin (**11**). The second group, believed to interfere with post-viral adsorption events, was made of monensin (**2**), salinomycin (**4**), lasalocid (**1**), nigericin (**5**), Dianemycin (**20**), alborixin (**11**), kijimicin (**39**), SF2361 (**43**), SF2324 (**44**) and SF2487 (**45**) [88]. Yamauchi *et al.* [87] working specifically with kijimicin (**39**), tested at concentrations of 0.08 – 10.0 μg/ml confirmed its lack of ability at interfering with the absorption step, as well as early stage of the replication, such as integration. It was proposed that kijimicin (**39**) acted by decreasing the infectivity of the virus, which was possibly accomplished by means of incomplete glycosylation of gp120 [87].

A dose-dependent study of the effect of monensin (**2**) on chronically infected MOLT-3/HTLV-IIIB revealed a marked inhibitory effect on the proteolytic processing of gpl60 to gpl20, after 7 h of exposure at 10 μM [89]. This effect was specific as no effect on the protein level of gag proteins $Pr53^{gag}$ p24 was noted. No effect on the expression of tat, vif and nef gene products was observed either. Monensin (**2**) also showed a marked reduction in the formation of syncytia at concentration > 3 nM when MOLT-3/HTLV-IIIB cells were co-cultured with CEM cell. Both effects were reversible if the cells were washed free of monensin (**2**) [89]. All these findings were later confirmed by a second group [90]. Laidlomycin (**29**) was also reported to induce a dose-dependent inhibition of HIV replication. The MOA of laidlomycin (**29**) was proposed to be via inhibition of gp120 expression. Laidlomycin (**29**) also induced an inhibitory effect on syncithium formation at concentrations as low as 1 μg/ml [92].

2.4.2 Activity against other types of viruses—Many carboxyl ionophores are reported to be active against several other DNA and RNA viruses: monensin (**2**), monensin B (**46**), nigericin (**5**), narasin (**3**), lasalocid (**1**), X-206 (**32**), septamycin (**7**), A 28695B (**47**) and A204 (**48**) were tested against transmissible gasteroenteritis coronavirus, Newcastle disease virus (NDV), infectious canine hepatitis virus and infectious bovine rhinotracheitis virus [1]. All these agents showed a significant activity against transmissible gasteroenteritis coronavirus, MIC ranging from 0.005 to 0.25 μg/ml. Nigericin (**5**), narasin (**3**) and A28695B (**47**) are effective against NDV with MIC ranging from 0.02 to 2.0 μg/ml. Only septamycin (**7**) was active against infectious canine hepatitis virus (MIC = 0.32 μg/ml). Monensin B (**46**), nigericin (**5**), narasin (**3**), X-206 (**32**), septamycin (**7**) and A204 (**48**) were effective against the infectious bovine rhinotracheitis virus, MIC ranging from 0.005 to 0.08 μg/ml [1].

2.5 Cytotoxicity and antiproliferative

Resistance to chemotherapy is a common clinical problem in patients with cancer. During treatment tumor cells or neoplastic cells are often found to be refractory to a variety of drugs with different structures or modes of actions. These cancers are referred to as MDR forms.

Most multidrug resistance is caused by *trans*-membrane xenobiotic transport proteins belonging to the superfamily of ATP-binding cassette (ABC) transporter efflux pumps [93,94].

Carboxyl polyethers are interesting antineoplastic drug candidates for several reasons and show potent antiproliferative activity *in vitro* and *in vivo.* Some carboxyl polyethers such as nigericin (**5**) have proven to be selectively cytotoxic inhibiting DNA replication of tumor cells *in vivo*. Another feature that makes carboxyl polyethers even more appealing as antineoplastic drug candidates is their ability to reverse multidrug resistance in human carcinoma. Carboxyl polyethers are reported as chemosensitizing agents. These molecules selectively increase the sensitivity of cancerous cells, but not normal cells, to several cytotoxic agents of which the clinically used anticancer drug paclitaxel [95].

Kawada *et al.* [42] evaluated the effects of several carboxyl ionophores on colchicine resistance in human carcinoma MDR KB-C410 [42]; these compounds were inostamycin (**24**), lysocellin (**15**), laidlomycin (**29**), monensin (**2**), dianemycin (**20**), leuseramycin (**26**), nigericin (**5**), lonomycin A&C (**17**, **22**), carriomycin (**8**), deoxy-salinomycin, antibiotic 6016 (**23**), SF2324 (**44**), SF2361 (**43**) and SF2487 (**45**). It was discovered that the cancer cells responded better to colchicine when some polyethers were added simultaneously. Laidlomycin (**29**), monensin (**2**), dianemycin (**20**) and leuseramycin (**26**) led to > 100-fold potentiation of colchicine cytotoxicity. The most active compound was laidlomycin (**29**); at 0.3 and 1 μg/ml, it potentiated cytotoxicity of KB-C4 cells by ~ 725-fold [42]. Compared to tumor cells, the potentiation of normal cells was negligible; the ratio of IC_{50} in the absence of polyether versus the IC_{50} in presence of polyether only varied in the range 0.4 – 2.4 μg/ml. Inostamycin (**24**) was also reported to have a chemosensitizing effect on paclitaxel in Ms-1 cell, small cell lung carcinoma. This effect was specific to these types of cells and to paclitaxel, as no potentiation was noted with other tested agents, driamycin, vinblastine, methotrexate, cisplatin, etoposide and camptothecin [95]. Inostamycin (**24**) was also reported to reverse multidrug resistance in these cell lines. Using radiolabeled vinblastine, Kawada *et al.* [96] established that MDR cells treated with inostamycin (**24**) (0.5 – 2 μg/ml) accumulated the drug. Inostamycin (**24**) (1 μg/ml) acted by inhibiting drug efflux [96].

Baibakov *et al.* [80] and Margolis *et al.* [97] studied the antineoplastic MOA of nigericin (**5**) and established that nigericin (**5**) was a unique type of cytostatic agent. The compound (**5**) acts not by interfering with spindle microtubules or transcription/translation processes directly, but rather by altering intracellular pH [80,97]. Nigericin (**5**) showed antiproliferative potential, as a cytostatic agent, in Ehrlich ascites carcinoma cells. The proposed MOA related to its ability to acidify the intracellular environment, a consequence of its H^+/K^+ anti-transport ability [97]. It is believed that by decreasing the pH DNA synthesis is halted. Near to 100% inhibition of the DNA synthesis was achieved at 0.5 μM nigericin (**5**), with the pH of the incubation medium being 7.0 [97]. An additional study utilizing an *in vivo* method such as tridimensional histocultures of human lung tissues, with normal cells present in the same histoculture, determined that this antineoplastic effect of nigericin (**5**) was selective. Nigericin (**5**) 10^{-6} M showed no effect, either on the histology of normal cells or on their DNA synthesis. However, in cancerous tissues the same concentration of nigericin (**5**) halted DNA synthesis in 67% of the cases, induced pyknotic

nuclei and dystropic alteration in 27% of tumor exposed to nigericin (**5**) and necrosis in 13% of cases. Another carboxylic polyether, ionomycin (**12**), is also reported to possess antineoplastic properties. It induced inhibition of the growth of a human bladder cancer cell line, HT1367, *in vitro* in a dose concentration gradient, 0.1 – 100 μg/ml, and time dependent, 10 μM of ionomycin (**12**), manner. The MOA here is reported to be the induction of apoptosis by means of the downregulation of Bcl-2 and upregulation of Bax. Ionomycin (**12**) was also effective *in vivo*, as it inhibited HT1367 tumor's growth [98].

2.6 Cardiovascular effects

Several carboxyl polyethers were reported to show ionotropic, chronotropic and hemodynamic properties. Because of the critical role of Ca^{2+} in cardiovascular contractile systems, this was predictable at least for those carboxyl polyethers that are selective for this ion, lasalocid (**1**) and A23187 (**13**). It is well established that that lasalocid (**1**), also known as X-537A, is a positive ionotropic agent. In canine studies, lasalocid (**1**) is able to increase the contractility index of the heart by approximately threefold at 2 mg/kg [3,7]. X-537A is also reported as a positive ionotropic and chronotropic agent in dogs. In barbiturated dogs, at dosage 2 mg/kg, it caused a threefold increase in the contractility as well as a modest rise in aortic pressure and heart rate. It also induced a drop in total peripheral resistance followed by a drastic increase in blood flow through the coronary arteries of the left ventricle [3]. The exact MOA through which these carboxyl polyethers induce contractility of cardiac muscle is still unclear. Initially, it was believed that this could be the result of their ability to shuttle Ca^{2+} and catecholamine across membranes. But this was refuted after the discovery that carboxyl polyethers specific to monovalent cations were able to induce, even more effectively, this type of response. Nonetheless, it is believed that catecholamine is partially involved because the effects of these molecules on the cardiac muscle is suppressed by β-adrenergic inhibitors.

Several other carboxyl ionophores were reported to possess a cardiovascular effect. Monensin (**2**) reportedly induced an increase of arterial blood pressure, myocardial contractility and total peripheral resistance when intravenously administered to anesthetized cats at a dose of 0.075 – 0.375 mg/kg [99]. Similar effect was observed when 0.125 – 2.00 mg/kg were administered via the same route to anesthetized dogs [99]. Monensin (**2**) was also effective on isolated organs; it showed a vasoconstrictor effect on isolated rabbit aortic strips at concentration ≤7 μg/ml and a myocardial stimulation effect in isolated rabbit hearts [99].

Three other carboxyl ionophores, grisorixin (**16**), alborixin (**11**), lonomycin A (**17**), are reported to have similar effects. Grisorixin (**16**) induced a coronary vasodilator effect in dogs at doses of 60 μg/ml; this was associated with a marked increase in the coronary blood flow, which reached a maximum at this concentration. At doses of 125 – 500 g/kg further inotropic and hypertensive effects were observed [101]. Grisorixin (**16**) was also reported to have a cardio-tonic effect on isolated perfused rat hearts [102]. In guinea pigs, grisorixin (**16**) and alborixin (**11**) 4 mg/kg/min i.v. are reported to increase blood pressure. The MOA is believed to be linked to their intrinsic ionophorous potential, via the ability of the molecules to alter the blood concentration of cations such as K^+ and Na^+ [103]. Moins *et al.*

[104] working with anesthetized dog reported similar findings, as 2 mg/kg of grisorixin (**16**) and 1 mg/kg of alborixin increased the ventricular contractile force and systolic and diastolic arterial pressures. This was associated with an increase in the plasma concentration of K^+ followed by a decrease in the concentration of Na^+ [104]. Owing to the reports of compounds such as grisorixin (**11**) inducing the release of catecholamine, the physiological response associated to the release of catecholamine was also proposed as a possible justification of the cardio vascular effects [101]. Lonomycin A (**17**), another carboxyl polyether, was also reported to induce a coronary vasodilatation effect in dogs. Its MOA was proposed to be the stimulation of the Na^+, K^+-ATPase activity [105].

As stressed by Pressman, and despite their toxicity, carboxyl polyethers are important drug leads for control of various cardiovascular conditions. Their value lies in their outstanding ionotropic, chronotropic and hemodynamic potential. These molecules could prove life-saving tools in controlling conditions such as failure owing to myocardial infraction and other similar forms of shock. Carboxyl polyethers such as lasalocid (**1**) (1 mg/kg) were proven effective at restoring dogs in cardiogenic shock. Similar data were reported for salinomycin (**4**) (0.15 mg/kg). According to Pressman, the narrower the transport spectrum of a molecule, the fewer the undesirable effects that are produced [3].

2.7 Other biological activities of carboxyl polyethers: immunoregulatory, herbicidal, anti-inflammatory

2.7.1 Immunoregulatory—Two measures are usually adopted to protect poultry against a variety of disease such as Angara disease virus (ADV) and NDV and promote growth. These include vaccination and addition of substances such as antibiotics, coccidiostat and vitamins to feed. Among additives approved at present are several carboxyl polyethers, lasaloicid (**1**), monensin (**2**), salinomycin (**4**) and manduramycin (**35**). There are some recent concerns about these additives and the possible association with vaccine failure in poultry. Few reports have actually proven that therapeutic agents such as cyclophosphamide and corticosteroids possess immunomodulatory properties.

Munir *et al.* in 1994 and 2007 studied the immunomodulatory effects of salinomycin (**4**) and monensin (**2**); specifically the effects of these molecules on the protective immune response in NDV and ADV vaccinated chickens. These authors established that unlike cyclophosphamide, salinomycin (**4**), at a dosage of 0.1 g/kg, did not adversely affect the bursal, splenic, thymic and liver weight gain [106]. It was also established that NDV vaccinated chickens that received salinomycin (**4**) 60 mg/kg of feed had higher antibiotic titers at days 14, 21, 28, 35, 42 compared to unmedicated chickens [52,106] or vaccinated chickens that were medicated with monensin (**2**) 12 mg/kg instead [52]. These salinomycin medicated chickens also gained significantly more weight, $p < 0.05$, compared to all the other groups evaluated. These chickens were challenged with both viruses ADV and NDV after vaccination. No post-ADV or post-NDV challenge mortality was observed in vaccinated chickens that received salinomycin (**4**) and no clinical sign of the disease was observed [52,106].

From these studies, it seemed that far from causing vaccine failure, carboxyl polyether such as salinomycin (**4**) actually seem to have a boosting effect on the anti-NDV and anti-ADV immune response [52,106].

Another carboxylic polyether reported as having immunoregulatory potential was ionomycin (**12**), a calcium-specific ionophore. Ionomycin (**12**) interferes with physiological processes by increasing the intracellular level of calcium, an effect that could have several implications on key cells of the immune system such as neutrophils and macrophages. They exert their action by production of microbicidal species such as superoxide anion via an NADPH-dependent process known as 'respiratory burst' in response to *in situ* triggers such as inflammatory agents. Ca^{2+} is documented as an enhancer of NADPH oxidase activity. Finkel *et al.* [107] reported that ionomycin (**12**) at a concentration of 1 – 10 nM can prime neutrophils to release approximately sevenfold more superoxide anion during stimulation. Ionomycin (**12**) was also reported to induce T cell activation [107].

2.7.2 Herbicidal—It has been reported that biological activities of nigericin (**6**) also possess herbicidal properties. A concentration-dependent study of the effect of nigericin (**5**) on the growth of the radicle of garden cress seed showed a dose-dependent inhibitory effect. A 50% reduction in the elongation was achieved at 1.3 – 2.0 μg/ml, the maximum inhibition was reported at ~ 3.33 μg/ml. Nigericin (**5**) did not induce browning or necrosis of tissues in the process [12].

2.7.3 Anti-inflammatory—Dianemycin (**20**) was recently reported as having topical anti-inflammatory potential on several animal models for cutaneous inflammation. In a croton-oil induction of ear edema, dianemycin (**20**) had a comparable activity to prednisolone, a potent steroidal anti-inflammatory with an ED_{50} of 0.8 versus 0.4 mg/ear. No anti-inflammatory activity was observed in the UV-induced erythema test or in the delayed type sensitivity test unlike the control, prenisolone. Additionally, no acute toxicity was observed with topical application ≤10 mg/ear [13].

3. Toxicity

Acute toxicity of the naturally occurring polyether ionophores is relatively specific to the organism that it is affecting. It is clear that minimal exposure to these very active compounds initiates some type of physiological response [7]. In the case of higher organisms and specifically mammals and birds, these effects are almost equally diverse [1]. For example, a common poisoning scenario is a horse consuming a small quantity of feed prepared with a ruminant's polyether antibiotic and dying rather quickly or wild turkeys consuming anticoccidial chicken feed and dying. Although the chirality of the central carboxylate of the molecules can predict inonophoric specificity, the respective LD_{50} acute toxicity values for individual species of molecules are equally diverse and unpredictable [79]. For example, LD_{50} ± SE values for an acute oral dose of monensin (**2**) were: mouse (m) 70.0 ± 9.0 mg/kg, (f) 96.0 ± 12.0 mg/kg; rat (m) 40.1 ± 3.0 mg/kg, (f) 28.6 ± 3.8 mg/kg; dog (m) > 20.0 mg/kg, (f) > 10.0 mg/kg; rabbit 41.7 ± 3.6 mg/kg; monkey > 160.0 mg/kg; chicken 200.0 mg/kg; cattle 26.4 mg/kg; sheep 11.9 ± 1.2 mg/kg; goat 26.4 ± 4.0 mg/kg; swine 16.7 ± 3.57; horse 2 – 3 mg/kg; trout > 1000.0 mg/kg [79]. "Dogs given a daily oral doses of 0,

1.25, 2.5, 5, or 7.5 mg/kg of monensin (**2**) for 1 year survived with no evidence of toxicity in the two lowest dose groups … Four generations of rats were continuously maintained on diets containing 0, 33, 50, or 80 ppm of monensin (**2**). Except for a decrease in body weight gain, there were no compound-related effects on reproduction or observed teratogenic effects" [79]. These same dosing conditions were evaluated for a 2-year period, with respect to the skeletal and cardiac muscles, with no increase in chronic lesions or neoplasms being detected [79]. Despite these maverick chemo-physical qualities of the ionophores, considerable numbers of toxicology studies have attempted to illustrate/translate the specific toxicology and pharmacology of the most common polyether ionophores to human health utilization [7].

4. Cardiac toxicity

Whether a monovalent or divalent ionophore is used, these molecules will disrupt the Ca^{2+} concentrations, either forming Ca^{2+} complexes or depolarizing the membrane potential, changing the H^+ concentrations in the mitochondria [4]. It is clear that Ca^{2+} is an essential ion in the physiological activities of composite functionality in the entire human body's daily functions. Cardiac function is especially sensitive to the roles of Ca^{2+} owing to the intrinsic functions of the ion and its role in muscular contractions; so, expectedly, potent effects of polyether antibiotics have been observed in mammalian cardiac studies [3,56,80–82,108]. Canine studies are accepted as the translative animal model for human cardiac response and for the effects of carboxylic polyether ionophores. These studies have shown that as little as 2 μg/kg i.v. can induce coronary dilation [108,109]. The concern for clinical applications of these ionophores is that persons with coronary heart's disease who have coronary arterial dilation, as part of the hearts own auto regulatory response to occlusion of coronary arterial vessels, will dilate the affected vessels further in the presence of an indiscriminate vasodilator. The unaffected vesicles would dilate further and the already maximally dilated obstructed vessels would divert the blood supply away from the ischemic regions of the myocardium. This phenomenon is called 'coronary steal' and has been observed in the administration of the drug dipyridamole, a thrombus inhibitor and chronic vasodilator [103,110]. As a large number of the population is affected by coronary heart disease these concerns have validity, although this phenomena was experimentally evaluated and the coronary steal was not observed [110].

Only recently have the *in vitro* tools been available for cardiac toxicity evaluations with respect to interaction on the *hERG* (human Ether-a-go-go Related Gene) gene and the associated $K_v11.1$ potassium ion channel that repolarizes the I_{Kr} current in the cardiac action potentials. The polyether antibiotics have not yet been critically evaluated in hERG assays. The drug interactions related to hERG ion channel were not mandated by ICH guidelines until November 2005 (mandate #CHMP/ICH/423/02). Consequently, the effects of carboxyl polyether ionophores on the QT_c with respect to the interaction with hERG have not yet been evaluated.

5. Conclusions

Carboxyl polyethers are broad spectrum antibiotics. They are active against a wide range of biological targets: bacterial, fungal, protozoan, viral, neoplastic and cardiovascular. A few authors have also reported carboxyl polyethers as immunomodulating agents. *In vitro*, these molecules have proven to be effective at very low concentrations. The malaria parasite (*P. falciparum*) is especially sensitive to several of these compounds with IC_{50} values in the nanomolar range. Based on the reports in this review it can be argued that carboxyl polyethers are highly selective. Unlike Gram negative bacteria or fungi for instance, Gram positive bacteria tend to be extremely sensitive to these antibiotics. Moreover, the IC_{50} values of several of these molecules against mammalian cells tend to be significantly higher, when compared to the IC_{50} against targeted etiological agents.

Despite these interesting features the only current application for carboxyl polyethers is in veterinary medicine, where they are used as controls for coccidiosis and feed absorption efficiency. The main obstacle for the use of carboxyl polyethers as drugs to control human diseases seems to be the issue of toxicity. With reductions in toxicity carboxyl polyethers possess some interesting qualities against serious threats such as MRSA and VRE and have proven to be more effective (*in vitro*) than drugs that are currently used clinically, such as vancomycin and oxacillin. They have also shown to be effective against several other resistant bacterial strains including penicillin resistance strains of *S. aureus*, tetracycline resistant strain of *Micrococcus sp*, aminoglycoside resistant strain of *Streptococcus faecalis*, and macrolides resistant strain of *Sarcina lutea*. Carboxyl polyethers have also proven effective at namomolar range against chloroquine resistant strains of *P. falciparum* and are more potent against these resistant strains than several currently marketed antimalarial drugs. Their mechanism of action against the malaria parasite appears uniquely different from that of the currently utilized drugs. This makes them possible candidates for use in combination therapy.

6. Expert opinion

On the basis of our assessment of the literature, polyether ionophores show a high degree of promise for the potential control of drug-resistant bacterial and parasitic infections. Many of these infectious diseases fall under the umbrella of neglected disease with limited options for therapeutic intervention. Furthermore, recent decades have emphasized the importance of combination therapies for the long-term control of disease and mitigation of resistance. The long history of the utilization of polyether ionophores as growth promoting antibiotics by the agricultural industry validates the potential cost-effective use of these drug products for other applications. The polyether antibiotics seem to provide reasonable oral availability, half-life, metabolic and general stability, absence of a UV sensitizing chromophore combined with significant potency. Despite the long history of use of the class, very limited medicinal chemistry and drug optimization studies have been reported, leaving the door open to these opportunities in the future. In many instances, the potency and *in vivo* efficacy for the control of bacterial and parasitic infections is truly remarkable. However, concerns about toxicity need to be addressed with further optimization and preclinical evaluation. On the basis of the available literature, there is still insufficient data to clearly classify these

molecules as either too toxic or safe as a class. Several carboxyl polyethers have indeed been shown to be too toxic in animal models for malaria but the results cannot be generalized to the entire class. Using an *in vivo* model for cancer, nigericin (**5**) was recently reported to be highly selective in targeting cancerous cells, broadening the scope of possible utility for this class [80]. As a result, an organized and carefully orchestrated identification and optimization of leads using *in vitro* models followed by an *in vivo* assessment of toxicity and efficacy would seem to yield viable drug candidates for the control of drug-resistant infectious diseases and cancer with a reasonable understanding of pharmacokinetics, stability and cost of goods. The reported toxicity for monensin (**2**) of > 160.0 mg/kg (LD_{50}) in primates and frequent utilization of this drug in agriculture makes the polyether class an attractive group of molecules for optimization and development of human health applications for the control of drug-resistant diseases such as malaria and MRSA.

Acknowledgments

Declaration of interest

Dion A Kevin II is supported by the MS/AL SeaGrant and National Institutes of Health. Damaris AF Meujo is supported by a fellowship from MMV (Medicine for Malaria Venture) and Triton Biopharma. Mark T Hamann is funded by NIH, NOAA/SeaGrant, MMV, Kraft Foods, and is a cofounder and significant shareholder of Triton Biopharma.

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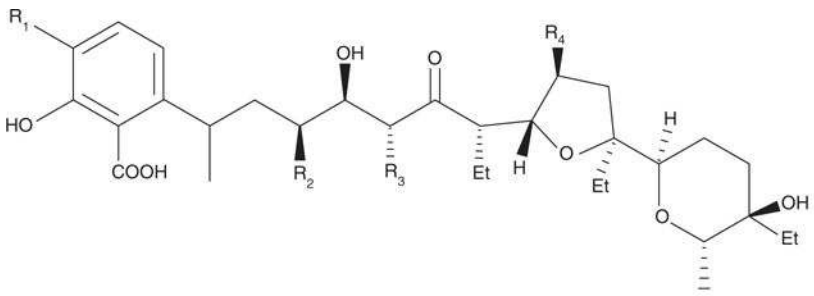
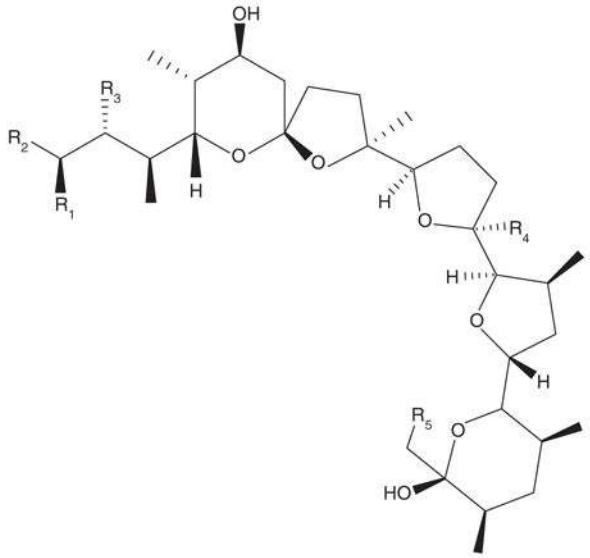
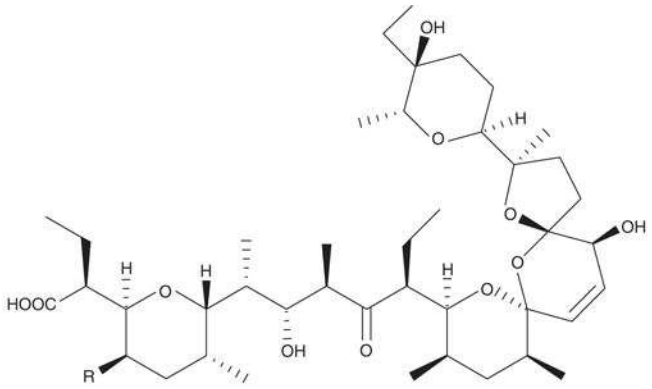


1 Lasalocid A, $R_1 = R_2 = R_3 = R_4 = CH_3$ [122]
67 Lasalocid B, $R_1 = C_2H_5$, $R_2 = R_3 = R_4 = CH_3$ [185]
68 Lasalocid C, $R_1 = R_3 = R_4 = CH_3$, $R_2 = C_2H_5$ [185]
69 Lasalocid D, $R_1 = R_2 = R_4 = CH_3$, $R_3 = C_2H_5$ [185]
74 Lasalocid E, $R_1 = R_2 = R_3 = CH_3$, $R_4 = C_2H_5$ [185]

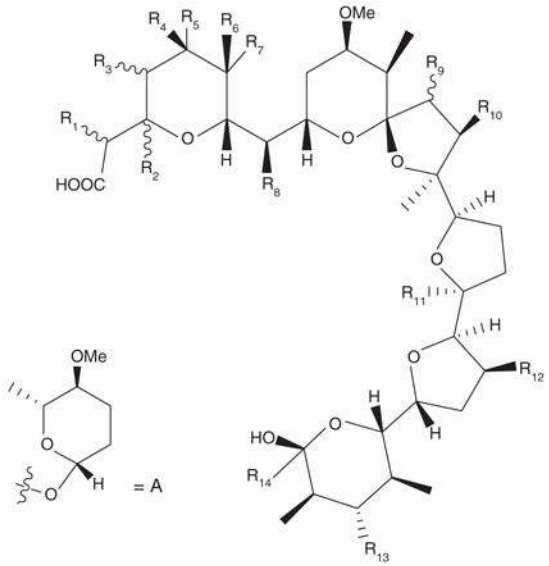


2 Monensin A, $R_1 = CH_3$, $R_2 = COOH$, $R_3 = OCH_3$, $R_4 = C_2H_5$, $R_5 = OH$ [115]
29 Laidlomycin, $R_1 = CH_3$, $R_2 = COOH$, $R_3 = COOC_2H_5$, $R_4 = CH_3$, $R_5 = OH$ [27]
46 Monensin B, $R_1 = CH_3$, $R_2 = COOH$, $R_3 = OCH_3$, $R_4 = CH_3$, $R_5 = OH$ [168]
70 26-Deoxy-Laidlomycin, $R_1 = CH_3$, $R_2 = COOH$, $R_3 = COOC_2H_5$, $R_4 = CH_3$, $R_5 = H$ [170]

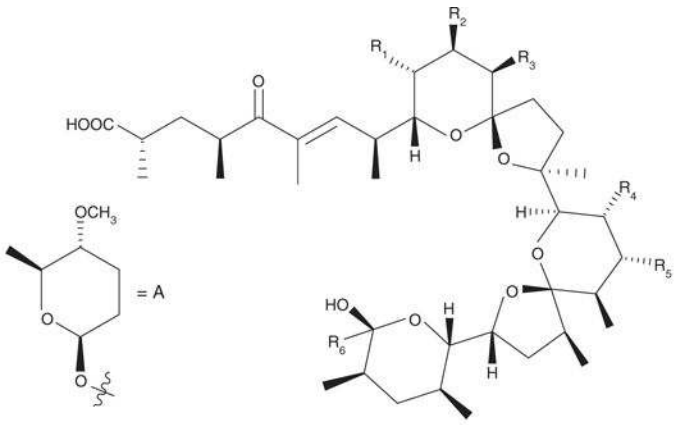
Figure 1a



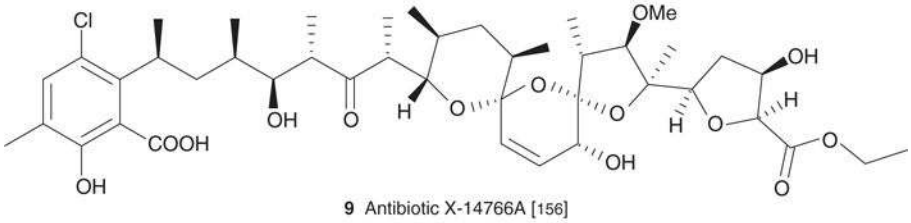
3 Narasin, R = CH_3 [188]
4 Salinomycin, R = H [184]



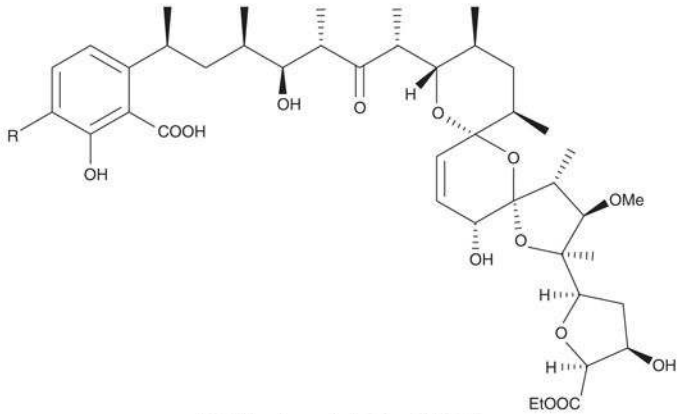
5 Nigericin $R_1 = \alpha CH_3$, R_2 = H, $R_3 = R_9 = \beta CH_3$, $R_4 = R_5 = R_6 = R_7 = R_8 = R_{10}$ = R_{13} = H, $R_{11} = R_{12} = CH_3$, $R_{14} = CH_2OH$ [81]
7 Septamycin $R_1 = R_9 = R_{14} = \alpha CH_3$, $R_2 = \beta OH$, $R_3 = \beta CH_3$, $R_4 = R_8 = R_{12} = R_{11} = R_{13}$ = H, $R_5 = R_{10} = OCH_3$, R_6 = A, $R_7 = CH_3$ [24]
8 Carriomycin, $R_1 = R_3 = \beta CH_3$, $R_2 = \beta OH$, $R_4 = R_6 = R_8 = R_{11} = R_{12} = R_{13}$ = H, $R_7 = R_{14} = CH_3$, $R_9 = \alpha CH_3$, R_5 = A, $R_{10} = OCH_3$ [138]
16 Grisorixin $R_1 = \alpha CH_3$, R_2 = H, $R_3 = R_9 = \beta CH_3$, $R_4 = R_5 = R_6 = R_7 = R_8 = R_{10} = R_{13}$ = H, $R_{11} = R_{12} = CH_3$, $R_{14} = \alpha CH_3$ [190]
33 K-41 A $R_1 = \alpha OH$, $R_2 = \beta OH$, $R_3 = \beta CH_3$, $R_4 = R_8 = R_{12} = R_{11}$ = H $R_5 = R_6 = R_{10} = OCH_3$, $R_7 = R_{14} = CH_3$, $R_9 = \alpha CH_3$, R_{13} = A [203]
36 CP-82,009 $R_1 = R_9 = R_{14} = \alpha CH_3$, $R_2 = \beta OH$, $R_3 = \beta CH_3$, $R_4 = R_8 = R_{11} = R_{12}$ = H, $R_5 = OCH_3$, R_6 = A, $R_7 = CH_3$, $R_{10} = R_{13} = OCH_3$ [57]
48 A-204 , $R_1 = R_7 = R_9 = \alpha CH_3$, $R_3 = \beta CH_3$, $R_2 = \beta OH$, $R_4 = R_8 = R_{11} = R_{12}$ = H, R_5 = A, $R_6 = R_{10} = R_{13} = OCH_3$, $R_{14} = CH_3$ [201]
61 Martinomycin $R_1 = \alpha CH_3$, $R_2 = \alpha OH$, $R_3 = \beta CH_3$, $R_4 = R_8 = R_{11} = R_{12}$ = H, $R_5 = R_6 = R_{10} = OCH_3$, $R_7 = R_9 = \alpha CH_3$, R_{13} = A, $R_{14} = CH_3$ [144]
65 CP-96,797 $R_1 = \alpha OH$, $R_2 = \beta OH$, $R_3 = \beta CH_3$, $R_4 = R_8 = R_{10} = R_{11} = R_{12}$ = H $R_5 = R_6 = OCH_3$, $R_7 = R_{14} = CH_3$, $R_9 = \alpha CH_3$, R_{13} = A [153]
78 K-41 B $R_1 = \alpha OH$, $R_2 = \beta OH$, $R_3 = \beta CH_3$, $R_4 = R_8 = R_{11} = R_{12}$ = H $R_5 = R_6 = OCH_3$, $R_7 = R_{14} = CH_3$, $R_9 = \alpha CH_3$, $R_{10} = R_{13}$ = A [202]



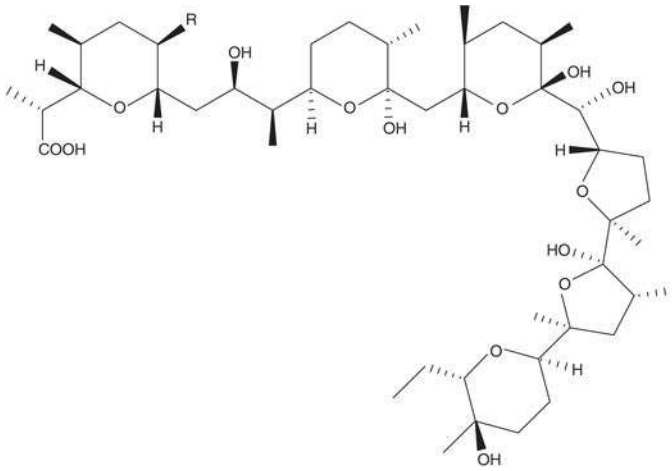
6 Lenoremycin, $R_1 = H$, $R_2 = A$, $R_3 = CH_3$, $R_4 = R_5 = H$, $R_6 = CH_2OH$ [135]
19 X14931A, $R_1 = CH_3$, $R_2 = OH$, $R_3 = R_4 = R_5 = H$, $R_6 = CH_2OH$ [199]
20 Dianemycin, $R_1 = CH_3$, $R_2 = OH$, $R_3 = R_4 = H$, $R_5 = A$, $R_6 = CH_2OH$ [108]
26 Leuseramycin, $R_1 = CH_3$, $R_2 = OH$, $R_3 = R_4 = H$, $R_5 = A$, $R_6 = CH_3$ [23]
71 Iso-Dianemycin, $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$, $R_5 = A$, $R_6 = CH_2OH$ [198]



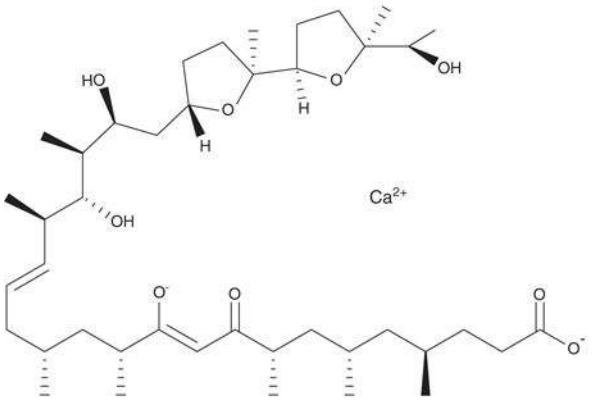
9 Antibiotic X-14766A [156]



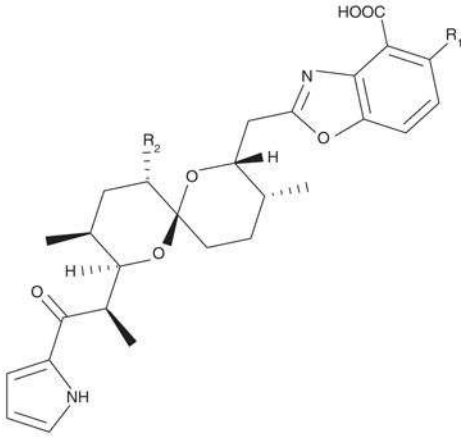
10 Noboritomycin A, R = CH_3 [25]
27 Noboritomycin B, R = C_2H_5 [25]



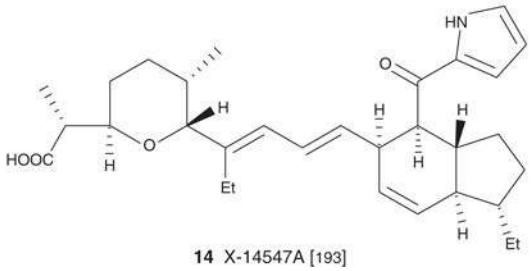
11 Alborixin, R = CH_3 [110]
32 X-206, R = H [194]



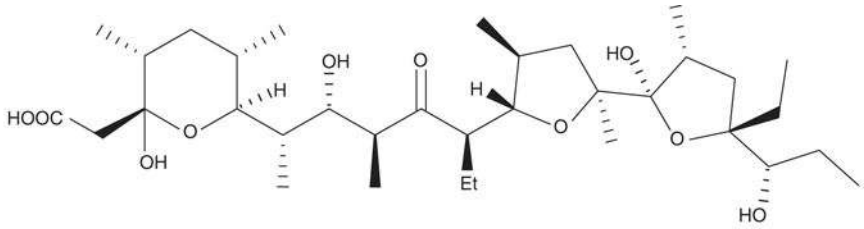
12 Ionomycin [189]



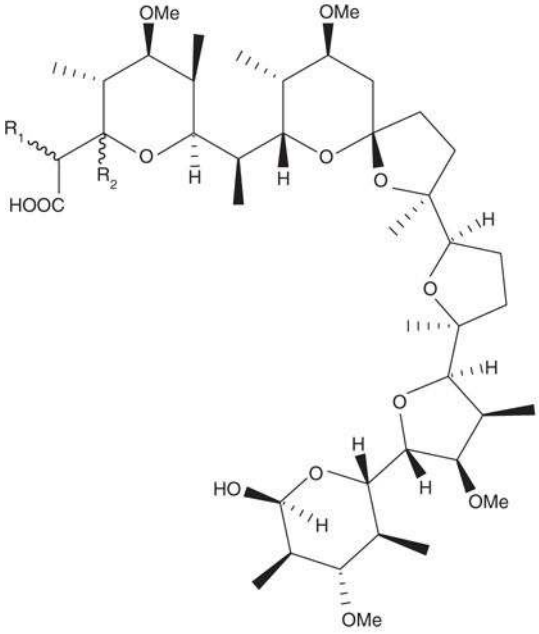
13 Calcimycin , R_1 = $NHCH_3$, R_2 = CH_3 [192]
30 X-14885, R_1 = OH, R_2 = H [150]
73 Cezomycin, R_1 = H, R_2 = CH_3 [181]



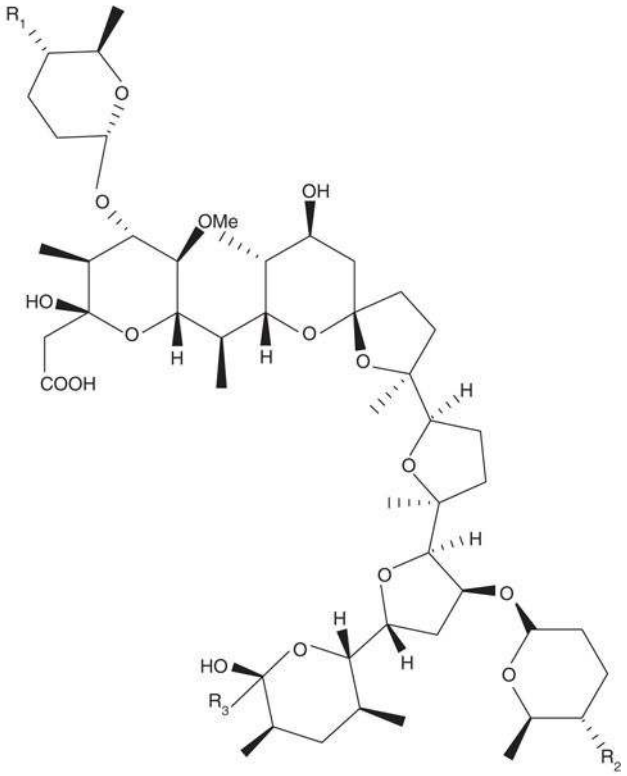
14 X-14547A [193]



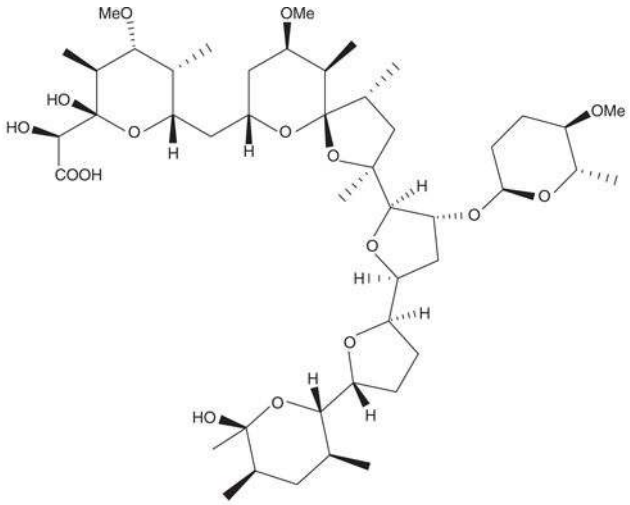
15 Lysocellin [140]



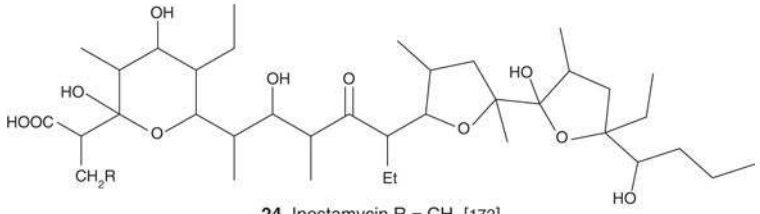
17 Lonomycin A $R_1 = \alpha CH_3$, $R_2 = \alpha OH$ [18]
21 Lonomycin B $R_1 = \alpha CH_3$, $R_2 = \beta OH$ [10]
22 Lonomycin C $R_1 = H$, $R_2 = \alpha OH$ [10]



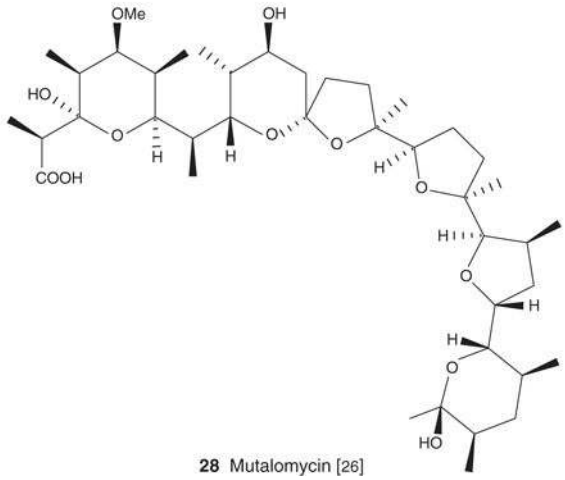
18 Octacyclomycin $R_1 = R_2 = OCH_3$, $R_3 = CH_2OH$ [19]
50 CP-91, 243, $R_1 = R_2 = OH$, $R_3 = CH_3$ [148]
66 UK-58,852, $R_1 = R_2 = OCH_3$, $R_3 = CH_3$ [207]
75 CP-91, 244, $R_1 = OH$, $R_2 = OCH_3$, $R_3 = CH_3$ [148]



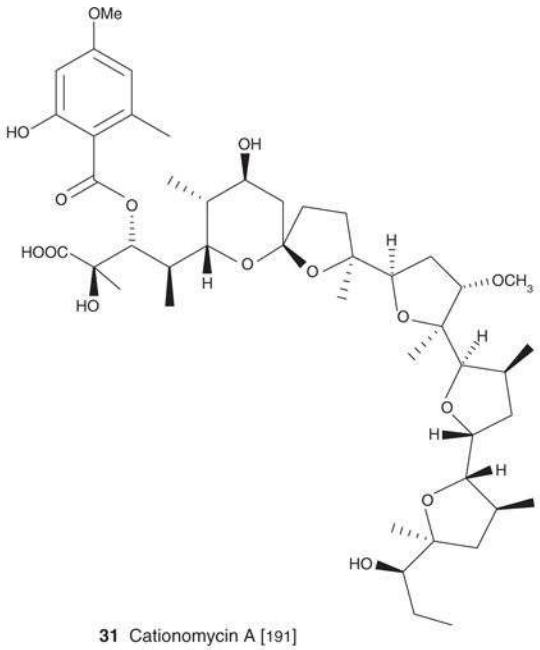
23 Antibiotic 6016 [20]



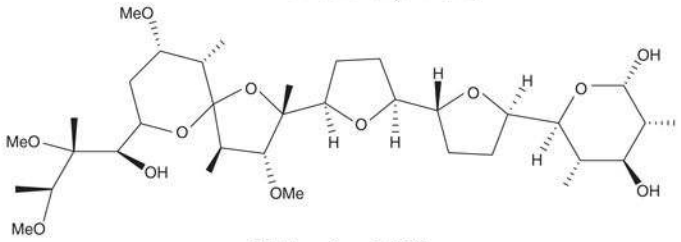
24 Inostamycin R = CH_3 [172]
25 Inostamycin B R = H [22]



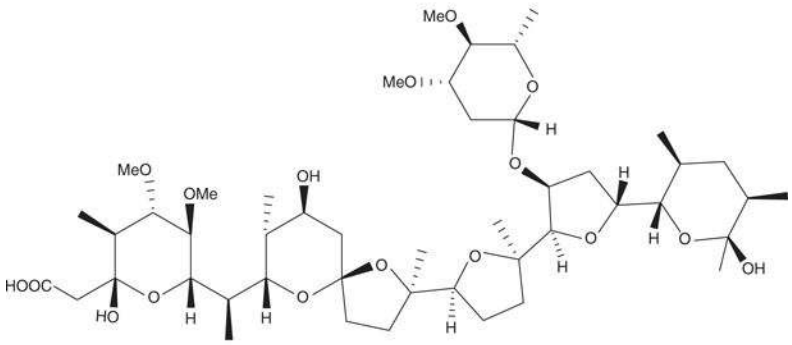
28 Mutalomycin [26]



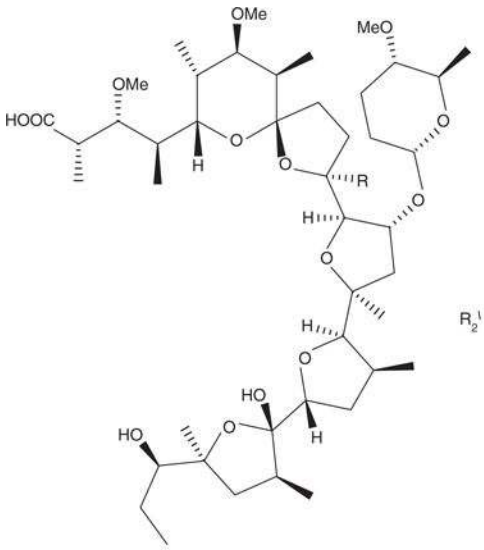
31 Cationomycin A [191]



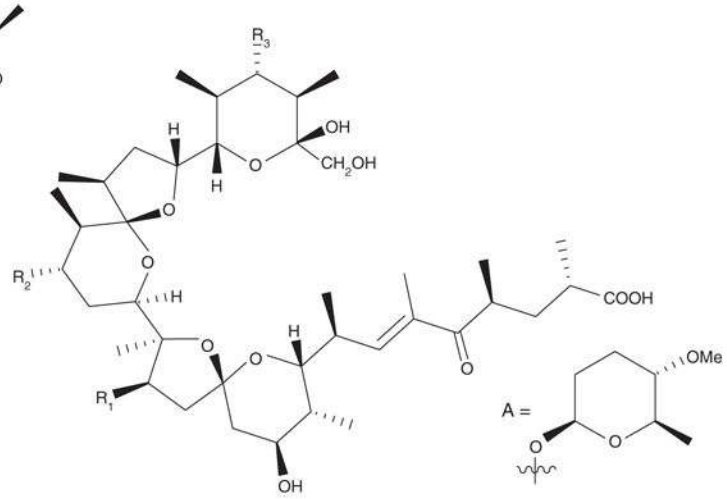
34 Hawaiimycin I [48]



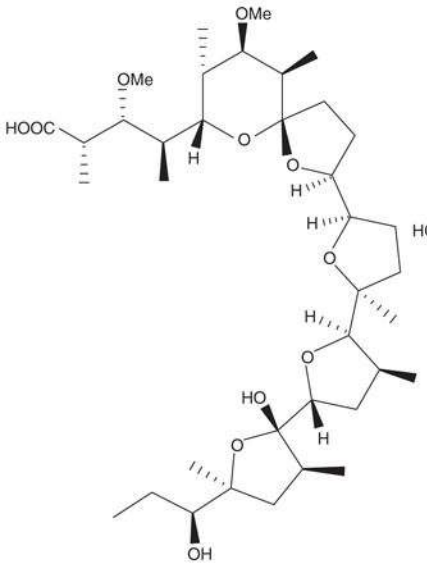
35 Maduramycin [70]



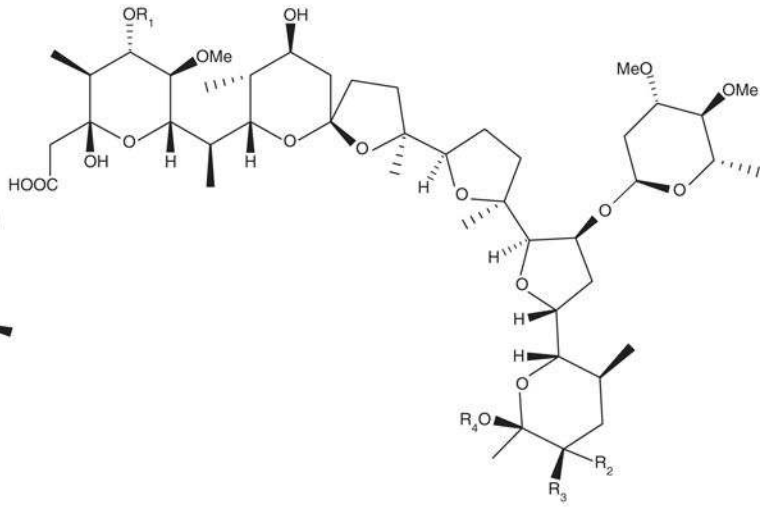
37 CP-84,657, R = CH_3 [54]
62 Portmicin, R = H [151]



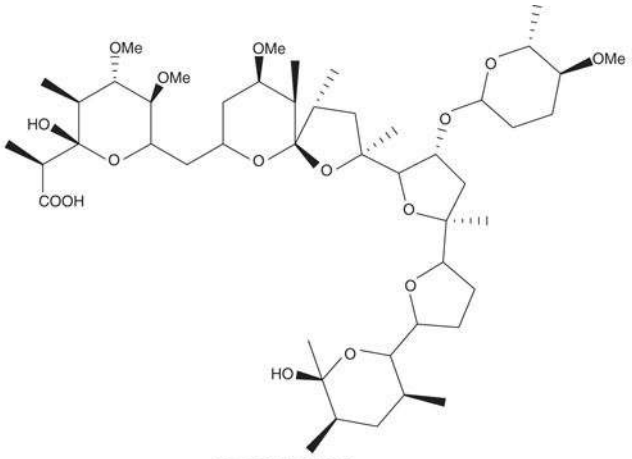
38 CP-80,219, $R_1 = R_2 = H$, $R_3 = A$ [55]
40 Endusamycin, $R_1 = A$, $R_2 = R_3 = H$ [58]



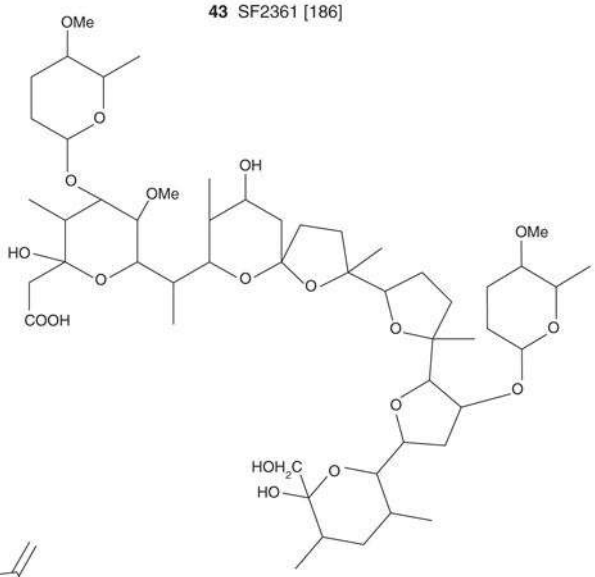
39 Kijimcin [56]



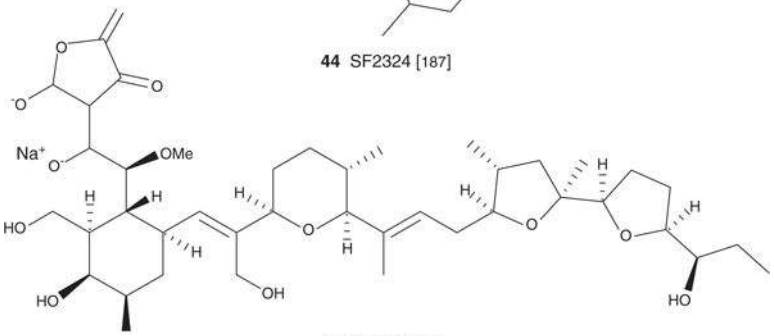
41 X-14868A $R_1 = CH_3$, $R_2 = H$, $R_3 = CH_3$, $R_4 = H$ [59]
42 X-14868B $R_1 = CH_3$, $R_2 = H$, $R_3 = CH_3$, $R_4 = CH_3$ [59]
58 X-14868C $R_1 = H$, $R_2 = H$, $R_3 = CH_3$, $R_4 = H$ [59]
59 X-14868D $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = H$, $R_4 = H$ [59]



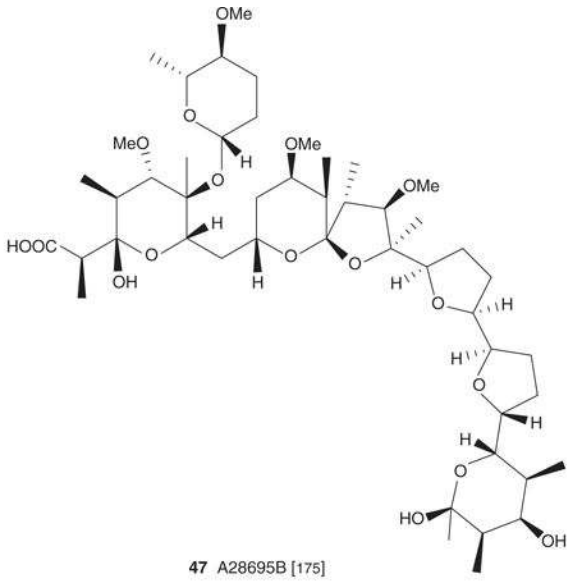
43 SF2361 [186]



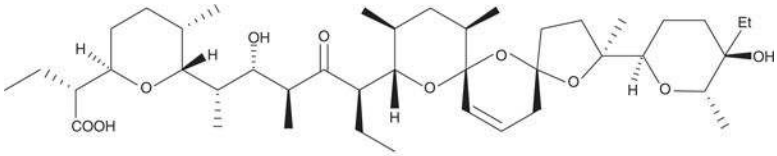
44 SF2324 [187]



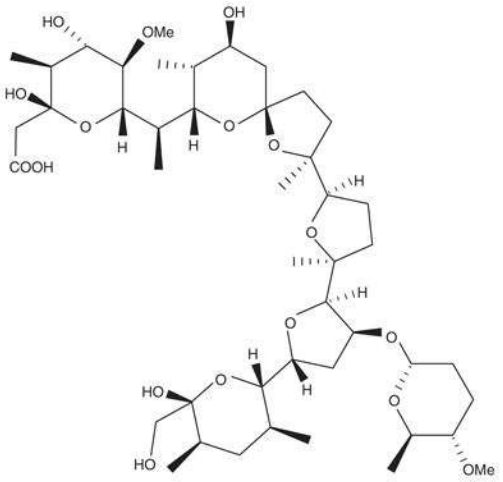
45 SF2487 [24]



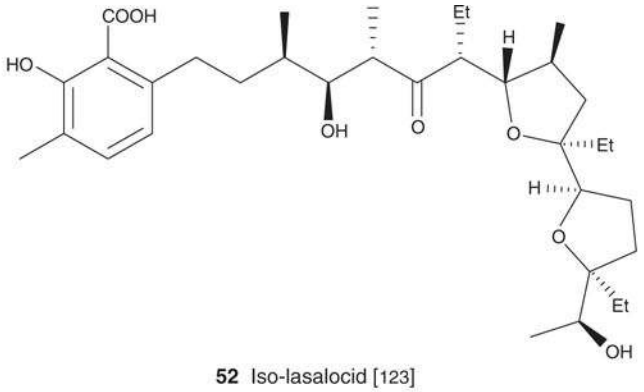
47 A28695B [175]



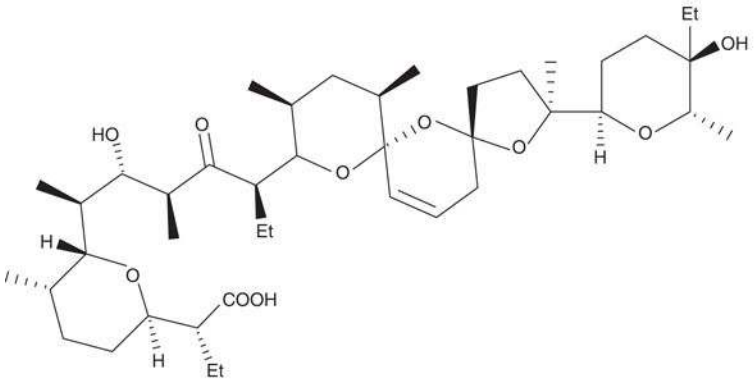
49 Deoxy-(*O*-8)-Salinomycin [146]



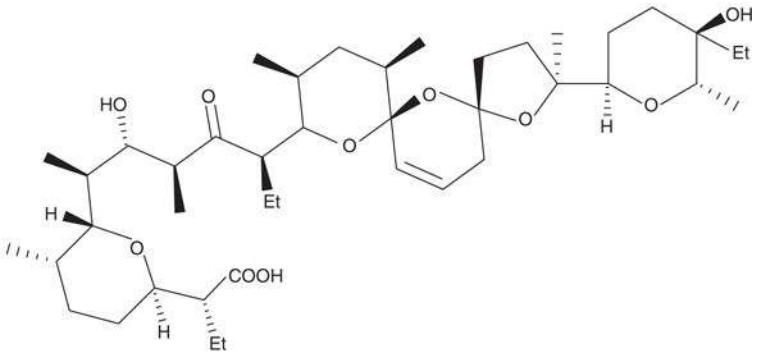
51 CP-120,509 [149]



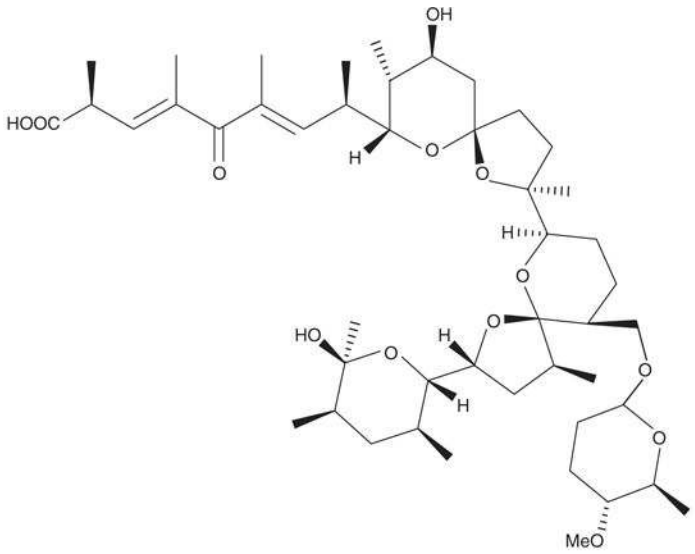
52 Iso-lasalocid [123]



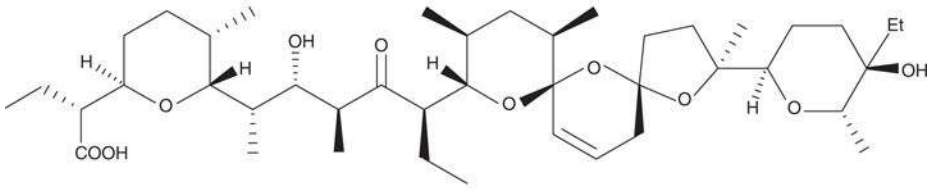
53 20-Deoxynarasin [143]



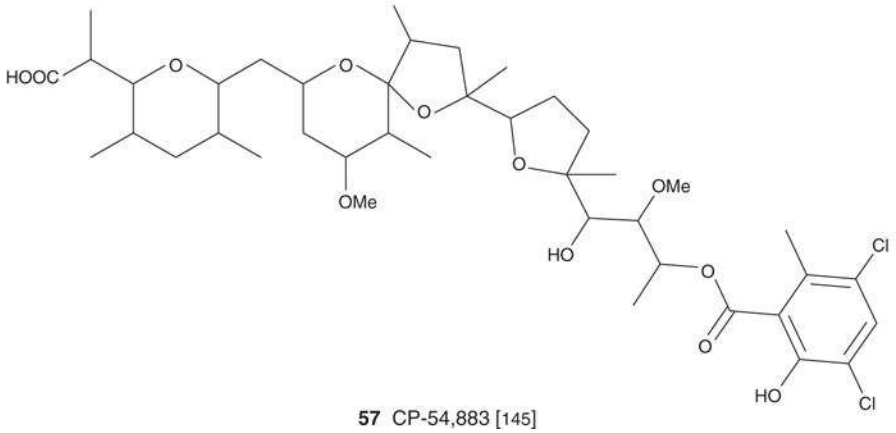
54 20-Deoxy-17- epi-narasin [143]



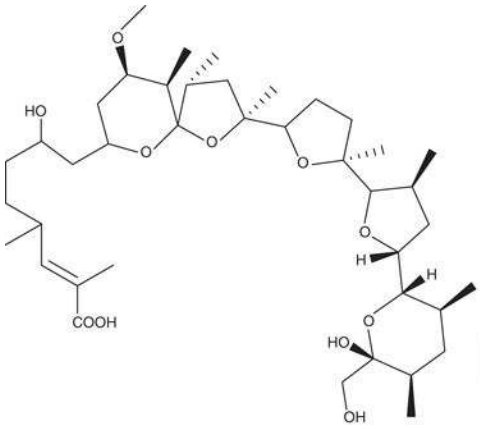
55 Moyukamycin [154]



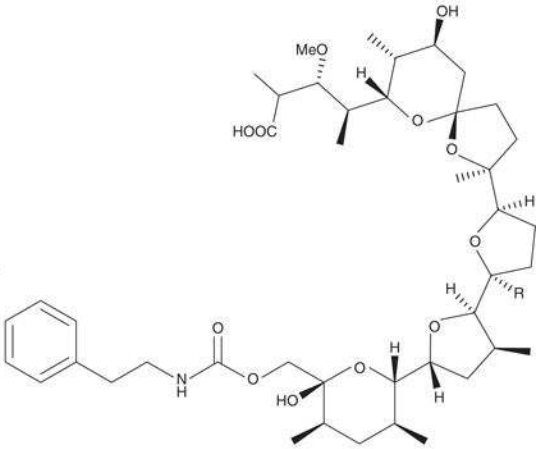
56 Deoxy-(*O*-8)-epi-17 -salinomycin [146]



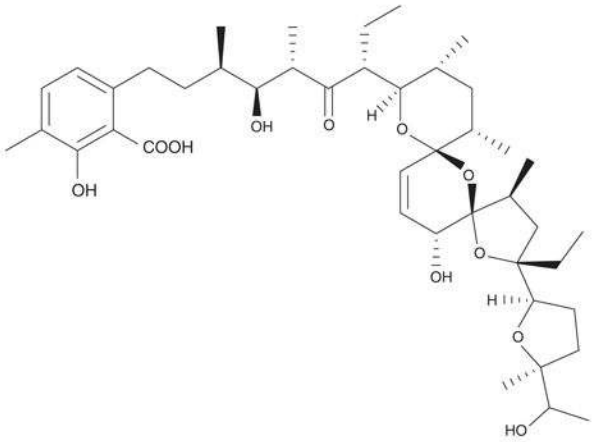
57 CP-54,883 [145]



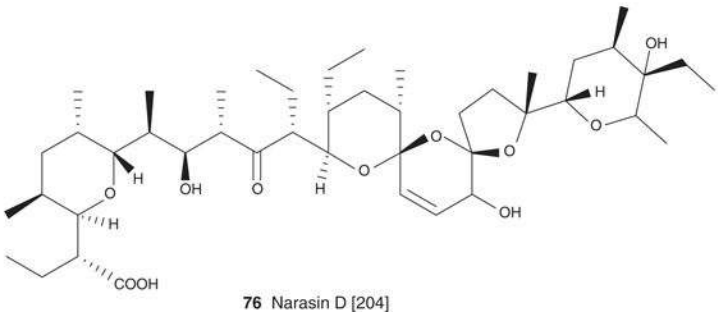
60 Abierixin [100]



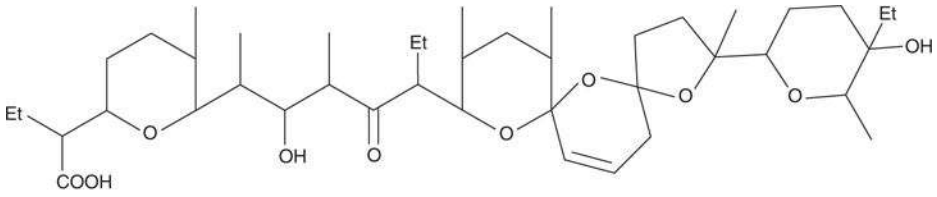
63 X-14667 A, R = CH_3 [152]
64 X-14667 B, R = C_2H_5 [152]



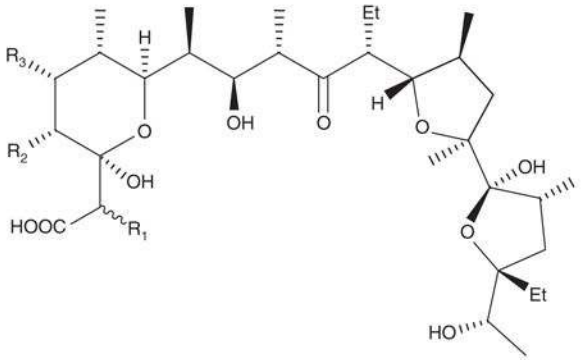
72 CP44161 [206]



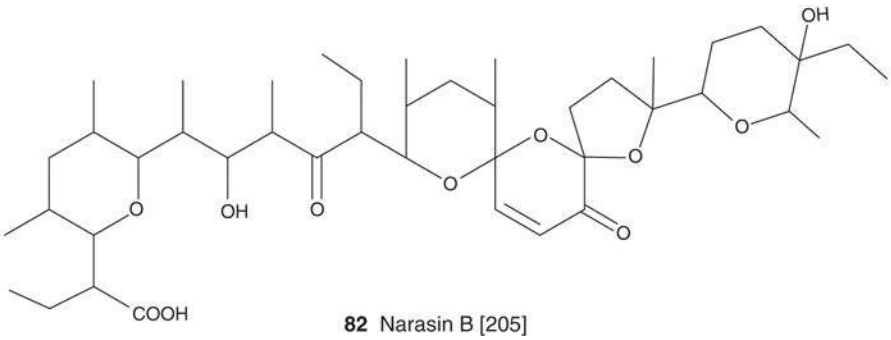
76 Narasin D [204]



77 Antibiotic SY-1 [196]

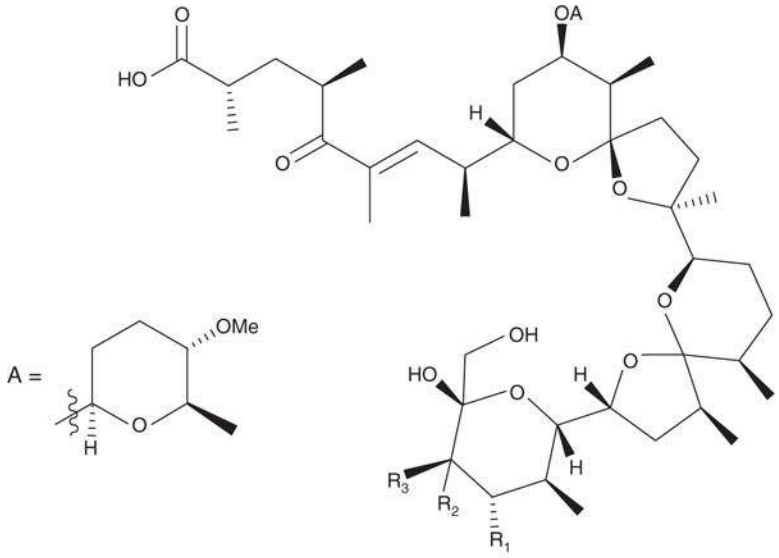


79 X-14889B, R_1 = βMe, R_2 = αCH_3, R_3 = H [182]
80 X-14889C, R_1 = H, R_2 = αCH_3, R_3 = H [182]
81 X-14873A, R_1 = H, R_2 = αC_2H_5, R_3 = OH [183]



82 Narasin B [205]

Figure 1b



83 A-130B R_1 = OA, R_2 = H, R_3 = CH_3 [178]
84 A-130C R_1 = H, R_2 = CH_3, R_3 = H [178]

Figure 1o

Figure 1. Structure of carboxyl polyethers

Scifinder and PubMed were the main search engines used to locate articles relevant to the topic presented in the present review. Keywords used in our search were specific names of each of the 88 compounds presented in the review as well as more general terms such as polyethers, ionophores, carboxylic polyethers and polyether antibiotics.

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Table 1

Overview of reported bioactive naturally occurring polyethers (from 1967 – 1994[*]), sources and their reported *in vivo* and *in vitro* testing.

Name (acronyms), molecular formula, molecular weight	Organism from which it was isolated	*In vitro* activities	Tested *in vivo*	Availability of crystal structure	Discovery year, journal, authors
Lasalocid A (**1**), $C_{34}H_{54}O_8$, 590.79	*Streptomyces lasaliensis NRRL 3382*	Antiparasitic [40,64,68,85], antiviral [88], antibacterial [1,119], antifungal [1,31]	Antimicrobial and/or antiparasitic effect [32,67,113,120,121]	[122]	[122]
Monensin A (**2**), $C_{36}H_{62}O_{11}$, 670.88	*Streptomyces cinnamonensis ATCC 15413*	Antiparasitic [38,40,65,76,85,111], antiviral [88,89,112], antibacterial [30,168], antifungal [1], antiproliferative/apoptotic [42,168]	Antimicrobial and/or antiparasitic effect [40,66,67,76,68,113,168], immunoregulatory effect [52], cardiovascular effect [99,114], Antiviral [134]	[115]	[115]
Narasin A (**3**), $C_{43}H_{72}O_{11}$, 765.03	*Streptomyces aureofaciens NRRL 5758*	Antibacterial [1,30,188], antifungal [1], antiparasitic [38,40,85]	Antiviral [134], antiparasitic [188]		[188]
Salinomycin (**4**), $C_{42}H_{70}O_{11}$, 751.00	*Streptomyces lasaliensis*	Antiparasitic [38,68,85], antiviral [88], antibacterial [1,30], antifungal [1]	Antimicrobial and/or antiparasitic effect [49,66,67,88,113,116,118], immunoregulatory effect [52,106]		[184]
Nigericin (**5**), $C_{40}H_{68}O_{11}$, 724.97	*Streptomyces hygrocopicus*	Antiparasitic [40,65,75], antiviral [88,112], antibacterial [1], antifungal [1], antiproliferative/apoptotic [42,80,97]	Antimicrobial and/or antiparasitic effect [40,41,72,78], effect on CNS tissues [14,79], antitumor [80], antiherbicidal/insecticidal [12], Antiviral [134]	[81]	[81]
Lenoremycin (**6**), $C_{47}H_{77}O_{13}Na$, 873.10		Antibacterial, antifungal [1] [135]		[135]	[135]
Septamycin (**7**), $C_{48}H_{82}O_{16}$, 915.16	*Streptomyces hygroscopicus NRRL 5678*	Antibacterial, antifungal [1,24], antiproliferative/apoptotic [24]	Antiparasitic [24,195], Antiviral [134]		[24]
Carriomycin (**8**), $C_{47}H_{80}O_{15}$, 885.15	*Streptomyces hygroscopicus*	Antiproliferative/apoptotic [42], antibacterial, antifungal [43]	Antimicrobial and/or antiparasitic effect [136,137]	[138]	[138]
Antibiotic X-14766A (**9**), $C_{43}H_{62}C_1O_{14}Na$, 861.40	*Streptomyces malachitofuscus* subsp. downeyi	Antibacterial antifungal [155]		[156]	[156]
Noboritomycin A (**10**), $C_{43}H_{63}O_{14}Na$, 826.96	*Streptomyces Noboritoensis NRRL 8123*	Antibacterial [25]	Antibacterial [25]		[25]
Alborixin (**11**), $C_{48}H_{84}O_{14}$, 85.18	*Streptomyces albus*	Antibacterial [1], antiviral [88], antiparasitic [38,85,109], anticocicidal [111]	Antimicrobial and/or antiparasitic effect [40,64,69], cardiovascular effect [103]	[110]	[110]
Ionomycin (**12**), $C_{41}H_{70}CaO_9$, 747.07	*Streptomyces conglobatus ATCC 31005*	Antiparasitic [38], antibacterial, antifungal [1,189], Antiproliferative/apoptotic [98,129]	Immunoregulatory effect [53,55,126–128], effect on CNS tissues [15]		[189]
Calcimycin (A23187) (**13**), $C_{29}H_{37}N_3O_6$, 523.62	*Streptomyces Chartreusensis*	Antiparasitic [38], antibacterial, antifungal [1,29]		[192]	[192]

Name (acronyms), molecular formula, molecular weight	Organism from which it was isolated	*In vitro* activities	Tested *in vivo*	Availability of crystal structure	Discovery year, journal, authors
X14547 A (**14**) 439.98		Antiparasitic [38]			[193]
Lysocellin (**15**), $C_{34}H_{59}O_{10}Na.1/2H_2O$, 659.81	*Streptomyces cacaoi*	Antiproliferative/apoptotic [42], antibacterial [17]	Antimicrobial and/or antiparasitic effect [137]	[140]	[140]
Grisorixin (**16**), $C_{40}H_68O_{10}$, 708.96	*Streptomyces griseus*	Antiparasitic [38], antibacterial [11] Antimicrobial	Antimicrobial and/or antiparasitic effect [85], Cardiovascular effect [102,103,130]	[28]	[28]
Lonomycin A (**17**), $C_{44}H_{76}O_{14}$, 829.07	*Streptomyces hygrocopicus*	Antibacterial [18], antiproliferative/ apoptotic [42], antiparasitic [38,40]	Antimicrobial and/or antiparasitic effect [125], cardiovascular effect [105]		[18]
Octacyclomycin (**18**), $C_52H_{88}O_{19}$, 1,016.24	*Streptomyces* sp.	Antibacterial, antifungal, antiproliferative/ apoptotic [19]			[19]
X-14931A (**19**), $C_{40}H_{66}O_{11}$, 722.95		Antibacterial [16,199], antifungal [199]	Antiparasitic [199]	[199]	[199]
Dianemycin (**20**), $C_{47}H_{78}O_{14}$, 867.12		Antiviral [88], antibacterial [8], antiproliferative/apoptotic [42]	Anti-inflammatory [13]	[108]	[108]
Lonomycin B (**21**), $C_{44}H_{75}O_{14}Na$, 851.07	*Streptomyces ribosidifi cus TM-481*	Antibacterial and antifungal [10]			[10]
Lonomycin C (**22**), $C_{43}H_{73}O_{14}Na$, 837.04	*Streptomyces ribosidifi cus TM-481*	Antiproliferative/apoptotic [42], antibacterial [10]			[10]
Antibiotic 6016 (**23**), $C_{46}H_{78}O_{16}$, 887.10	*Streptomyces albus*	Antibacterial, antiparasitic [20]		[91]	[91]
Inostamycin (**24**), $C_{38}H_{68}O_{11}$, 700.94	*Streptomyces* sp. *MH816-AF15*	Antiproliferative/apoptotic [21], Antibacterial [22]		[171]	[171]
Inostamycin B (**25**), $C_{37}H_{66}O_{11}$, 687.01	*Streptomyces* sp. *MH816-AF15*	Antibacterial, antifungal [22]			[22]
Leuseramycin (**26**), $C_{47}H_{78}O_{13}$, 851.10	*Streptomyces hygroscopicus TM-531*	Antibacterial, antifungal [23]			[23]
Noboritomycin B (**27**), $C_{44}H_{65}O_{14}Na$, 840.99	*Streptomyces noboritoensis NRRL 8123*	Antibacterial [25]	Antiparasitic [25]		[25]
Mutalomycin (**28**) S-11743 $C_{41}H_{69}O_{12}$, 754.99	*Streptomyces mutabilis*	Antiparasitic [26]			[26]
Laidlomycin (**29**) AB-78 $C_{37}H_{62}O_{12}$, 698.88	*Streptoverticillum eurocidium*	antiproliferative/apoptotic [27,42] Antibacterial [27,30,119], antiviral [92]			[27]
X-14885 (**30**), $C_{27}H_{31}N_2O_7Na{\cdot}H_2O$, 536.57	*Streptomyces* sp. X-14885	Antibacterial, antifungal [150]		[150]	[150]

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Name (acronyms), molecular formula, molecular weight	Organism from which it was isolated	*In vitro* activities	Tested *in vivo*	Availability of crystal structure	Discovery year, journal, authors
Cationomycin A (**31**), $C_{45}H_{70}O_{15}$, 851.03	*Actinomadura azurea* sp. *Nov*	Antiparasitic [38], antibacterial [1,191]	Antiparasitic [191]		[191]
AntibioticX-206 (**32**), $C_{47}H_{82}O_{14}H_2O$, 889.15	*Streptomyces* sp.	Antiparasitic [39]	Antimicrobial and/or antiparasitic effect [39,132,133] cardiovascular effect [131]	[194]	[194]
K-41-A (**33**), $C_{48}H_{82}O_{18}$, 947.15	*Streptomyces gypseum NRRL 11168*	Antiparasitic [139], antibacterial [203]	Antiherbicidal/insecticidal [141]	[142]	[203]
Hawaiimycin I (**34**), $C_{36}H_{64}O_{12}Na$, 711.42	*Streptomyces* sp.	Antiparasitic [48]			[48]
Maduramycin (**35**) $C_{47}H_{80}O_{17}$, 917.13	*Actinomadura rubra*	Antibacterial [70] Antiparasitic [85,157]	Antimicrobial and/or antiparasitic effect [50,67,69]		[70]
CP-82,009 (**36**), $C_{49}H_{84}O_{17}$, 945.20	*Actinomadura* sp. (ATCC 53676)	Antibacterial [57]	Antiparasitic [57]	[57]	[57]
CP-84,657 (**37**), $C_{45}H_{78}O_{14}$, 843.09	*Actinomadura* sp.	Antibacterial [54]	Antiparasitic [54]	[54]	[54]
CP-80,219 (**38**), $C_{47}H_{78}O_{14}$, 867.13	*Streptomyces hygroscopicus*	Antibacterial [55]	Antiparasitic [55]	[55]	[55]
Kijimicin (**39**), $C_{37}H_{64}O_{11}$, 684.90	*Actinomadura* sp. MI215-NF3	Antibacterial [56], antiviral [86–88], antiparasitic [82]	Antiparasitic [56]	[56]	[56]
Endusamycin (**40**), $C_{47}H_{77}O_{14}Na$, 889.17	*Streptomyces endus* subsp. aureus (ATCC39574)	Antibacterial [58]	Antiparasitic [58]	[58]	[58]
X-14868A (**41**), $C_{47}H_{80}O_{17}$, 917.13	*Nocardia* X-14868	Antibacterial, antifungal [59]	Antiparasitic [59]		[59]
X-14868B (**42**), $C_{48}H_{82}O_{17}$, 931.15	*Nocardia* X-14868	Antibacterial, antifungal [59]	Antiparasitic [59]		[59]
SF 2361 (**43**), $C_{48}H_{82}O_{16}$, 915.16	*Actinomadura* sp. *SF-2361*	Antiviral [88], antiproliferative/apoptotic [42]			[186]
SF2324 (**44**), $C_{52}H_{88}O_{19}$, 1017.25		Antiviral [88,120], antiproliferative/ apoptotic [42]			[187]
SF 2487 (**45**), $C_{42}H_{63}O_{12}Na$, 805.00	*Actinomadura sp SF2487*	Antibacterial [124], antiviral [88,124], antiproliferative/apoptotic [42], antiparasitic [82]		[124]	[124]
Monensin B (**46**) $C_{35}H_{60}O_{11}$ 656.84	*Streptomyces cinnamonensis ATCC 15413*	Antiviral [1]		[166]	[200]
A 28695B (**47**) $C_{48}H_{82}O_{17}Na$, 953.54	*Streptomyces albus NRRL 3883*		Antiparasitic [195], Antiviral [134]		[195]

Name (acronyms), molecular formula, molecular weight	Organism from which it was isolated	*In vitro* activities	Tested *in vivo*	Availability of crystal structure	Discovery year, journal, authors
A-204 (**48**) $C_{49}H_{84}0_{17}$, 944.12	*Streptomyces albus*	Antiviral [1]		[201]	[201]
Deoxy-(0-8)-salinomycin (**49**), $C_{42}H_{70}0_{10}$, 735.00	*Streptomyces albus ATCC 21838*	Antibacterial, antifungal [146]		[146]	[146]
CP-91,243 (**50**), $C_{50}H_{83}O_{18}Na$, 995.10	*Actinomadurra roseorufa*	Antibacterial, antiparasitic, antifungal [148]			[148]
CP-120,509 (**51**), $C_{45}H_{76}O_{17}$, 889.10	*Actinomadura roseorufa*	Antibacterial, antifungal [149]	Antiparasitic [149]	[149]	[149]
Iso-lasalocid (**52**), $C_{34}H_{54}O_8$, 590.79	*Streptomyces lasaliensis*	Antibacterial [123]		[123]	[123]
20-Deoxynarasin (**53**), $C_{43}H_{72}O_{10}$, 743.00	*Streptomyces aureofaciens* NRRL 11181	Antibacterial, antiviral [143]	Antiparasitic [143]		[143]
20-deoxy-epi-17-narasin (**54**), $C_{42}H_{70}O_{10}$, 735.01	*Streptomyces aureofaciens* NRRL 11181	Antibacterial, antiviral [143]	Antiparasitic [143]		[143]
Moyukamycin (**55**), $C_{47}H_{75}O_{13}Na$, 871.10	*Streptomyces hygroscopicus* TM-581 (FERM-BP 274)	Antibacterial, antifungal [154]			[154]
(Deoxy-(O-8)3)-epi-l7 salinomycin (**56**), $C_{42}H_{70}O_{10}$, 735.01	*Streptomyces albus ATCC 21838*	Antibacterial, antifungal [146]	Hypertension [147]	[146]	[146]
CP-54,883 (**57**), $C_{41}H_{61}O_{12}Cl_2$, 817.83	*Actinomadura routienii Huang* sp.	Antibacterial, antiparasitic [145]			[145]
X-14868C (**58**), $C_{46}H_{78}O_{17}$, 903.10	*Nocardia* X-14868	Antibacterial, antifungal [59]	Antiparasitic [59]		[59]
X-14868D (**59**), $C_{47}H_{80}O_{17}$, 917.13	*Nocardia* X-14868	Antibacterial, antifungal [59]			[59]
Abierixin (**60**), $C_{40}H_{68}O_{11}$, 724.96	*Streptomyces albus NRRL B-1865*	Antibacterial, antifungal [100]	Antiparasitic [100]		[100]
Martinomycin (**61**), $C_{49}H_{84}O_{17}$, 967.50	*Streptomyces salvialis*	Antibacterial [144]	Antiherbicidal/insecticidal [144]		[144]
Portmicin (**62**), $C_{44}H_{76}O_{14}$, 829.07	*Nocardiopsis* sp. *No. 6270*	Antibacterial, antifungal [151]	Antiparasitic [151]		[151]
X-14667 A (**63**), $C_{44}H_{69}NO_{12}$, 804.02	*Streptomyces cinnamonensis*	Antibacterial, antifungal [152]			[152]
X-14667 B (**64**), $C_{45}H_{71}NO_{12}$, 818.04	*Streptornyces cinnamonensis*	Antibacterial, antifungal [152]			[152]
CP-96,797 (**65**), $C_{47}H_{80}O_{17}$, 917.15	*Streptomyces* sp.	Antibacterial, antifungal [153]	Antiparasitic [153]	[153]	[153]

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Name (acronyms), molecular formula, molecular weight	Organism from which it was isolated	*In vitro* activities	Tested *in vivo*	Availability of crystal structure	Discovery year, journal, authors
UK-58, 852 (**66**) $C_{52}H_{88}O_{18}$ 001.24	*Actinomadura roseorufa Huang* sp. nov., ATCC 39697	Antiparasitic, antibacterial [207]			[207]

*The most recent report on the discovery of these molecules that we came across.

Table 2

HIV-1 infectivity and cytotoxicity.

Compounds	Acute infection (H9)			Chronic (U937)		
	EC_{90} (μg/ml)	IC_{50} (μg/ml)	IC_{50}/EC_{90}	EC_{90} (μg/ml)	IC_{50} (μg/ml)	IC_{50}/EC_{90}
Monensin (**2**)	4.22 ± 2.6	13.44 ± 2.8	3.18	0.5 ± 0.25	0.59 ± 0.19	1.18
Salinomycin (**4**)	0.4 ± 0.04	6.98 ± 2.9	17.63	0.09 ± 0.02	0.28 ± 0.05	3.14
Lasalocid (**1**)	2.37 ± 2.9	48.80 ± 4.7	20.63	0.2 ± 0.2	1.35 ± 0.35	6.92
Nigericin (**5**)	0.68 ± 0.46	14.46 ± 8.0	21.26	0.05 ± 0.33	0.4 ± 0.007	8.32
Dianemycin (**20**)	7.12 ± 4.4	78.40 ± 4.7	11.01	1.1 ± 0.14	1.1 ± 0	1.00
SF2361 (**43**)	0.64 ± 0.36	49.10 ± 4.6	76.72	1.35 ± 0.49	2.1 ± 0.14	1.56
SF2324 (**44**)	> 100	> 100	> 1.00	3.7 ± 0.71	10.1 ± 0.14	2.73
SF2487 (**45**)	0.49 ± 0.18	7.8 ± 1.3	15.92	0.03 ± 0.15	1.85 ± 0.28	64.91
Alborixin (**11**)	2.5 ± 1.1	13.50 ± 3.1	5.4	0.12 ± 0.04	0.80 ± 0.28	6.53
Kijimicin (**39**)	1.63 ± 1.9	18.62 ± 11	11.41	0.1 ± 0.007	0.55 ± 0.07	5.79
Dextran Sulfate	< 1	> 100	> 100	NT		

From Nakamura *et al.*, 1992.

EC_{50}: Concentration that inhibits reverse transcription activity by 50% (viral replication); IC_{50}: Concentration that decreases cell viability by 50%.