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PHARMACEUTICAL LIPID FORMULATIONS OF AMPHOTERICIN B FOR THE TREATMENT OF HUMAN LEISHMANIASIS

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Abstract

The first description of a skin lesion, "Delhi button" dates back to Cunningham (1885) who reported the presence, on tissue sections, of bodies of 12.6 µm x 8.8 µm, presumably parasitic macrophages, containing "nucleoid bodies" which he believed to be spores belonging to Mycetozoa. But the first to describe the Leishmania parasite was, in 1898, a young man Russian military surgeon, named Borowsky. He investigated the cause of the "Sart button" at the military hospital in Tashkent. This paper, through the analysis of the studies carried out over the years proposes a description of the different therapeutic strategies for the treatment of leishmaniasis (advantages and criticalities of the same) and in particular an analysis detailed description of Amphotericin B, its mechanisms of action and pharmaceutical formulations, especially liposomal ones.

Keywords: *Amphotericin B, Leishmaniasis, Pharmaceutical lipid formulations, Amphotericin B in lipid complex (ABLC); Liposomal Amphotericin B (LAMB); Amphotericin B in colloidal dispersion (ABCD)*

Introduction

Apparently unaware of the previous works he described, on smears and sections of, numerous small corpuscles of 1.5 µm in diameter containing a nucleus and a "process" that started from the nucleus to the periphery of the body. Later Leishman (1903), examining the body of a young soldier in service in Dum-Dum (Calcutta) and died 38 hours earlier, he noticed injuries from dysentery in the colon and a large congested spleen, the pulp of which it contained a huge amount of ovoid or rounded bodies of 2-3 µm in diameter. Just 3 years later, Professor of Pathology in London examining a dead rat experimentally infected with African trypanosomes, he noticed the similarity of the bodies previously observed with degenerate rat trypanosomes. He concluded that the bodies observed in the soldier's spleen could be degenerate trypanosomes.

Leishman was therefore the first to describe the causative agent of visceral Leishmaniosis and to recognize its relationship with trypanosomes. In 1903 Donovan, after reading Leishman's article, examining splenic biopsy smears of a 12-year-old Indian suffering from irregular fevers, that malarial parasites in the blood, observed bodies which he believed to be neither splenic artifacts nor degenerated trypanosomes, he searched in vain for trypanosomes circulating in his blood.

Also in the same year, Laveran and Mensil examining the slides shipped from Donovan concluded that the observed bodies were erythrocyte parasites e they proposed the name of *Piroplasma donovani*. Donovan's own slides were observed by Ross (1903) who criticized the conclusions of Laveran and Mesnil concluding that the parasites were superimposed to erythrocytes and recalled involutional forms of trypanosomes. Ross described the parasite and proposed belonging to a new genus, named Leishmania sporozoa class. With the progress of technological innovation and significant developments in the field pharmaceutical new formulations have been created, more and more sophisticated, such as liposomes and nanoemulsions which improve the characteristics pharmacokinetics of the molecule have managed to make it even more effective the action of amphotericin B. By its very nature, Leishmaniasis remains a complex disease and insidious, difficult to identify especially in the initial stages, where it would be appropriate to intervene for a resolution of the same.

Therefore prevention is absolutely essential, especially in endemic areas (such as Italy and the Basilicata region itself) and in the areas of world where the incidence of disease in humans is very high (Third Countries World and developing countries). We must therefore, first of all, act on the environment: the environment preferred by sand flies consists of the crevices of the ground, the cracks in the walls, in humid atmospheres and above all characterized by the absence of winds [1].

A correct and timely diagnosis of Leishmaniasis is essential importance in order to start the appropriate therapy and to avoid any worsening of the pathology. It is important to proceed, first of all, with an adequate differential diagnosis from part of the medical staff and then proceed to more accurate and in-depth tests diagnostic [2].

The clinical suspicion of cutaneous leishmaniasis arises from the examination of the characteristic of the injuries, from the previous history of a stay in endemic countries e from the proven resistance to antiseptic and antibiotic treatments. Confirmation will be given by direct demonstration of the parasite using different techniques: cytodiagnostic, histological and cultural examination, analysis electrophoresis of isoenzymes, polymerase-chain-reaction (PCR) techniques e immunomarkers with monoclonal antibodies [2].

Pharmacological therapy

Over the past decade research on treatments for visceral leishmaniasis and cutanea had as its goal to use molecules more effectively already existing, both as monotherapy and in combination of drugs.

Systematic research in the various areas of the world, where the disease is endemic, have clearly shown that there is no universal treatment for leishmaniasis.

In South Asia, for example, enormous progress has been made in the eradication of the kala-azar

with precise strategies on first and first treatments second line with liposomal amphotericin B (Figure 1) and, in particular, the co-administered treatment of paromomycin (Figure 2) and miltefosine (Figure 3).

In East Africa sodium stibogluconate (SSG) and paromomycin in combination offer an advantage that can be compared to monotherapy with SSG, although not exempt from limitations, since this therapy requires 17 days of double infusions, very painful, and there is a risk of SSG-related cardiotoxicity (Figure 4).

However pharmacokinetic studies have led to better understanding of the mechanisms underlined, such as under-exposure of children treatment with miltefosine, and an improvement of the regimen using an allometric dosage [3].

The first agents to be used in the treatment of leishmaniasis, starting from the years Twenties of the last century, were the pentavalent antimony compounds, in two possible formulations, sodium stibogluconate (SSG) and meglumine antimoniate (MA) (Figure 5) [3]. One of the first countries to use it was Italy [1]. SSG was mainly used in the Indian subcontinent and East Africa while, antimonial compounds are concentrated in the cells of the reticuloendothelial system in which leishmaniasis are engulfed, and interfere with the metabolism of parasite through a selective inhibition action of some important enzymes glycolysis and β-oxidation of fatty acids (phosphofructokinase e pyruvic dehydrogenase) localized in glycosomes, with a consequent reduction of production of ATP and GTP.

Another possible action relates to the permeability and transport of cell membrane of the parasite. At the beginning of the 21st century the only alternative for the treatment of patients who did not give response to antimonials or for the treatment of relapses was the polyene antibiotic amphotericin B deoxycholate, very effective but required hospitalization prolonged for 15 or 20 intravenous infusions (doses from 0.75 to 1.0 mg / kg / day, daily or every other day always for 15 or 20 doses), with the monitoring of severe and common effects of nephrotoxicity and hypokalaemia. Due to its poor safety profile this drug is only usable for hospital administration.

In 2002 miltefosine, an orally taken alkyl phospholipid, was introduced into the assortment of anti-Leishmaniasis drugs, thus opening up to new ones more optimistic therapeutic scenarios [3]. Miltefosine, analogue of alkylphosphocholine, was the first drug administered orally to show adequate therapeutic efficacy in treatment of visceral leishmaniasis, albeit lower than that of amphotericin B. The most common therapeutic scheme provides a dose of 2.5 mg/kg/day for one treatment of about 28 days.

The most frequently shown side effects include and diarrhea, vomiting, increases liver enzymes and nephrotoxicity [4-9].

Furthermore, its use is not recommended in women of childbearing age, unless it is use contraception during treatment and for at least 6 months after treatment [2].

Miltefosine can be used in co-therapy with liposomal formulations of amphotericin B (LAMB 5 mg/kg and miltefosine 50 mg BID for 7 days). The one with miltefosine has proved to be one of the most effective treatments, where the conventional therapies failed [10].

Sitamaquine is an 8-amino-quinolinic antileishmaniasis agent orally administered, who has completed Phase II clinical trials for visceral leishmaniasis in India and Kenya (Figure 6).

Fexinidazole is an antiprotozoal agent discovered by Hoechst in 1970 and was then re-evaluated as a possible promising candidate for treatment of African human trypanosomiasis (HAT) by DNDi (Drugs for Neglected Diseases initiative) (Figure 7).

In vitro studies have demonstrated the leishmanicidal activity of fexinidazole and of its two main metabolites (fexinidazole sulfoxide and fexinidazole sulfone). Thanks to the advantage of oral administration and its safety profile, the combination of fexinidazole and miltefosine is being evaluated for the treatment of visceral leishmaniasis in East Africa.

Polyenes were, after griseofulvin (Figure 8), the first antifungals introduced on market and well over

200 compounds have been discovered since then same class.

At the end of the 1950s they represented a turning point against fungal infections, in particularly those systemic and invasive and still represent today first-choice drugs against life-threatening fungal infections [11-14].

Generally speaking, this class of molecules has a hydrophobic portion, represented by the double bonds which takes the name of "tail" and a portion hydrophilic, represented by a mycosamine molecule and a polyol chain containing seven hydroxyl groups.

Due to its amphipathic nature, amphotericin B appears to be poorly soluble in water and although initially the treatment on infected mice seemed to have success, no positive human results had been obtained.

Since the discovery of amphotericin B, many derivatives and formulations have been developed different (as well as liposomal formulations of the same Amphotericin) also to counteract the effects of high dose-dependent toxicity that characterizes polyene (topic discussed below) and its effects nephrotoxic as well as complications related to its. However, amphotericin B can still be regarded as one of the most effective drugs broad spectrum fungicides on the market and limited incidence of resistance development [11, 15-17].

To date, polyenes are regularly used, not only in the treatment of deep fungal infections but also, as in the present case, in the treatment of zoonoses such as leishmaniasis, both visceral and topical proving, albeit not the drug of first choice, certainly the most effective.

The peculiarity of this class of antifungals, however, is the elegance of the mechanism of action: polyenes, in fact, unlike antibacterial or other chemotherapeutic agents antifungals do not have a real pharmacological target, such as an enzyme or a cellular organelle, but interact with a fundamental molecule for the very existence of the cell, such as the phospholipid components of cell membrane (ergosterol, cholesterol and lanosterol) present not only in the fungal ones but also in the protozoan ones of the various species of Leishmaniasis [11].

Polyenes are able to alter the permeability of the membrane itself by reacting with sterols. Currently there are four models proposed to explain the mechanism of action: the pore forming model is the most studied. "Pore forming" is the most studied action model and involves the formation of a real "pore" inside the membrane of the fungal wall and/or protozoan.

Ergosterol interacts with polyene to form a complex similar to a ion channel that allows the escape of ions and small organic molecules and eventually leading to the death of the cell itself.

While the hydrophobic "tail" of the molecule binds to ergosterol (and therefore direct towards the lipid portion of the membrane) the hydrophilic polyols would form a aqueous channel stabilized by the intramolecular bonds between the groups of the "heads" hydrophilic of neighbouring molecules.

Since the length of amphotericin B is almost similar to that of membrane phospholipids, two types of channel can be created:

(1) a full pore consisting of two ring complexes;

(2) a "half pore" containing a single polyene ring.

Both types have the same type of structure, but the "half pore" one it would induce a conformational thinning of the bilayer lipids.

The presence of one or the other structure depends mainly on the type of polyene, by the composition and thickness of the membrane.

Pores only form when a certain concentration of polyene is reached in the membrane; below this threshold, complexes are formed aggregates called “non-aqueous pores” or “cation-selective pores” which can increase the permeability of the membrane to monovalent cations, while the "real" or "semi pores" can also allow the passage of other electrolytes and of larger molecules. Therefore, the greater the concentration of polyene, the greater the size of the channel that will be formed. Amphotericin B forms relatively large pores (with a diameter of about 0.46 nm) which can allow the passage of molecules of big dimensions [11].

Amphotericin B Formulations: conventional and innovative drug delivery forms

Amphotericin B deoxycholate: The first formulation of amphotericin B to be introduced to the market a starting from 1958 it was amphotericin B deoxycholate (Figure 9) [18]. In the traditional pharmaceutical formulation, amphotericin B is linked to sodium deoxycholate due to its poor solubility in the aqueous medium [19].

Following intravenous administration, amphotericin B dissociates from sodium deoxycholate, binds to plasma lipoproteins and accumulates in the spleen and in the liver.

Amphotericin B is over 90% bound to serum proteins and even if it is extensively metabolized, a certain amount is slowly eliminated with the urine over several days (the serum half-life is about 15 days). There administration, as a micellar suspension [27,28], takes place by slow drip within approximately 2 o'clock and 6 hours (depending on the dose administered) with the usual precautions observed for intravenous therapy.

The limitations related to the use of Amphotericin B deoxycholate concern in numerous side effects, which can be acute or chronic: acute symptoms are related to the infusion that causes the release of pro-inflammatory cytokines and chemokines such as IL-1β, TNF-α, MCP1 AND MIP-1β leading to fever, chills, generalized malaise, nausea, vomiting [20].

To reduce these undesirable effects, amphotericin B was deoxycholate encapsulated within lipid formulations that still maintain the their antifungal activity.

Liposomal formulations of amphotericin B: The use of liposomal formulations has proven to be better in the treatment of visceral leishmaniasis in HIV-infected patients; has been observed, in patients treated with Amphotericin B deoxycholate (and already in therapy with AZT and DDI) one appearance of petechiae in the lower limbs, which necessitated suspension of therapy.

The consequent use of the liposomal formulations did not cause the appearance of these side effects in therapy and allowed to induce remission complete clinic after 4 weeks [21].

The liposomal formulations of amphotericin B follow this principle: the drug is incorporated within a bilayer structure, composed of phospholipids and cholesterol [20].

Liposomes act as carriers (drug transporters) by reducing this way the non-specific binding of the drug to human cell membranes, conveying it to the cell walls containing a greater amount of ergosterol (whether fungal or protozoal).

This link allows a reduction in toxicity but also the use of higher doses high of the same drug. [11, 22-28]

In addition, the slow release of the drug from the lipid carrier ensures that the drug it does not bind to plasma proteins or LDL but remains in monomeric form. This makes it possible to increase the antifungal activity and decrease the toxicity in humans. [11, 20]

The improvement in effectiveness consists in the fact that Leishmaniasis are parasites obligate endocellular cells and the drug encapsulated within the liposome has such as target the phagocytic mononuclear system. [29]

Three types of lipid formulations are available:

1) Amphotericin B in lipid complex (ABLC);

2) Liposomal Amphotericin B (LAMB);

3) Amphotericin B in colloidal dispersion (ABCD) which differ from each other by different characteristics, particularly in their lipid composition, the their shape, their pharmacokinetic behaviour and, most importantly, their effects collateral [11, 30].

Amphotericin B in lipid complex (ABLC):

The lipid complex (Amphotericin B Lipid complex, ABLC) was the first of the series of lipid formulations containing amphotericin B [28]. The formulation consists of a suspension of Amphotericin B complexed with phospholipids dimyristoylphosphatidylcholine (DPCM) and dimyristoylphosphatidylglycerol (DMPG) in a molar ratio of 7: 3 (DMPC: DMPG = 7: 3) [11, 28].

The particles show a ribbon shape ranging in length from 1600-6000 nm in length. The amphotericin B/lipid ratio is 1:3. In terms of treatment efficacy, it is comparable to that of traditional formulation of amphotericin B but several studies have shown a high improvement of the safety profile.

Liposomal amphotericin B (LAMB):

Liposomal amphotericin is an encapsulated formulation of amphotericin B in unilamellar vesicles of 60-80 nm in diameter composed of phosphatidylcholine of 21 hydrogenated soy, cholesterol and distearoylphosphatidylglycerol and combined with amphotericin B in molecular ratio 2:0.8:1:0.4 [27, 31-35].

The drug is marketed in lyophilized form in a dose of 50 mg of antifungal/vial [11]. After intravenous administration, liposomes remain physicochemically intact for an extended period of time, increasing the plasma concentration [27].

Studies have suggested that the liposomal particles carry amphotericin B to the cells of the pathogen through the fusion of these with the cell membranes of the pathogen itself, leading to the death of the pathogen.

A high concentration in the liver and spleen was noted, considering that renal and pulmonary concentrations are much lower than those of traditional formulations of amphotericin B [11].

The latest frontiers in research are directed towards the realization of topical formulations and in this sense micro and nanotechnology are tools important, as they can be useful for modulating the release profile of drugs by improving the bioavailability of the drug at the site of action.

Some recent studies aim at the development of O/A nanoemulsions (NEs); these the latter are an interesting system, especially for low-solubility drugs and low permeability such as amphotericin B, increasing the permeation of the drug in the layer of the dermis.

The use of clove oil as an oily phase was based on its different properties already known pharmacological, including anti-leishmaniasis. The amphotericin B nanoemulsions thus developed have been shown to have relevant features:

1) stability during 365 days of refrigeration at 4° C;

2) very slow release of the active ingredient *in vivo*;

3) slow permeation of the drug during *ex vivo* tests.

This may indicate that nanoemulsions, as a topical treatment, are free of systemic effects.

Amphotericin B in colloidal dispersion (ABCD):

The colloidal dispersion of amphotericin B is composed of a bilayer of cholesterol sulphate, a naturally occurring metabolite in which polyene is found inserted in an equimolar relationship to form a highly organized structure:

two molecules of amphotericin B bind two molecules of cholesterol sulphate forming a tetramer which possesses a hydrophilic and a hydrophobic moiety; these tetramers aggregate in a spiral arm forming a structure discoidal with a diameter of about 122 nm and a thickness of 4nm [36, 37].

Conclusions

The discovery and introduction of amphotericin B into therapy represented one turning point in the history of the pathology. The great advantage lies in the effectiveness of its action mechanism which it also prevents the development of relevant forms of resistance by the protozoan if, however, it is not possible to ignore its high nephrotoxicity.

To reduce the impact of the latter, they have been since the 90s of the last century made several liposomal formulations of amphotericin B; these allow the accumulation of the drug in the macrophages of the endothelial reticulum system subtracting it from the plasma volume and reducing its renal distribution.

All treatments for the treatment of leishmaniasis require the drug to be administered by injection: intravenous for visceral and mucocutaneous forms, intralesional for the cutaneous one; if for the former this is the only solution possible, the most recent studies have demonstrated the efficacy and safety

of topical formulations for the cutaneous form; this represents a further strategy to reduce systemic side effects. The nanoemulsions technology has shown excellent stability, a slow one release of the active ingredient and high activity against promastigotes; among these, SinaAmpholeish, developed by the Mashhad University of Medical Science in Iran in 2019 gave promising results.

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Figure 1. Structure of Amphotericin B.

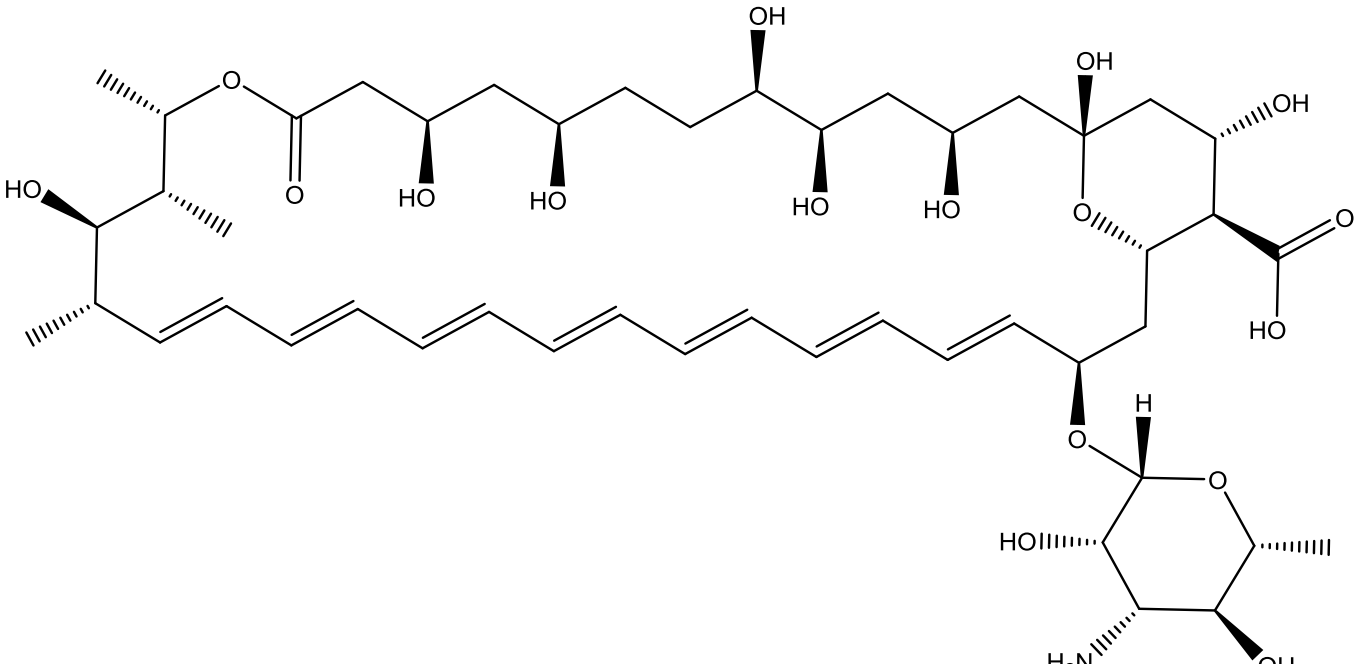

Figure 2. Structure of paromomycin.

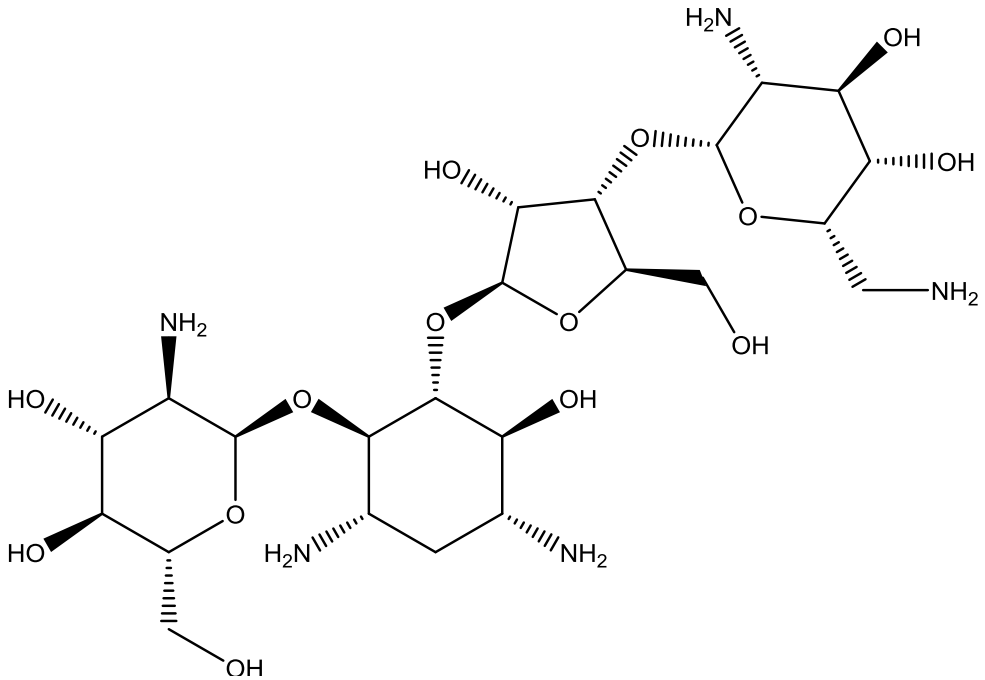

Figure 3. Structure of miltefosine.

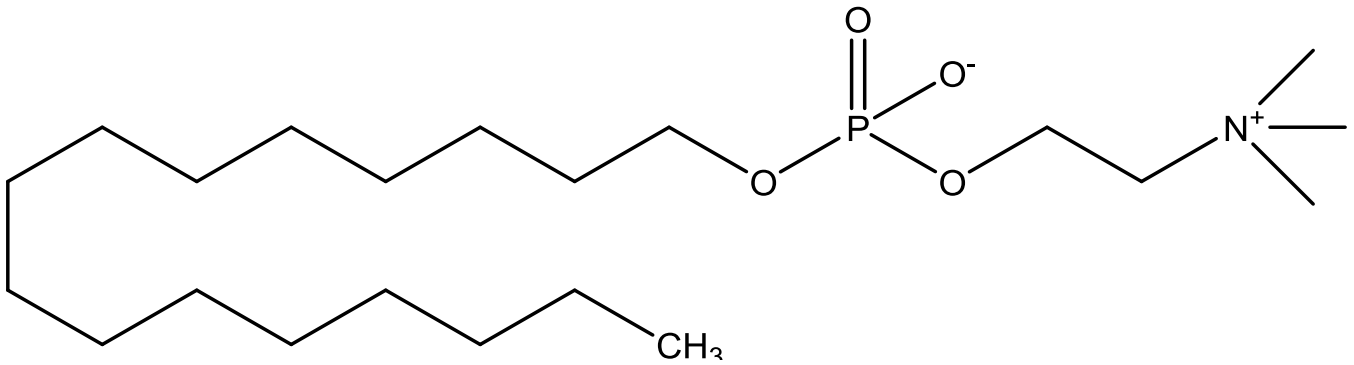

Figure 4. Structure of sodium stibogluconate.

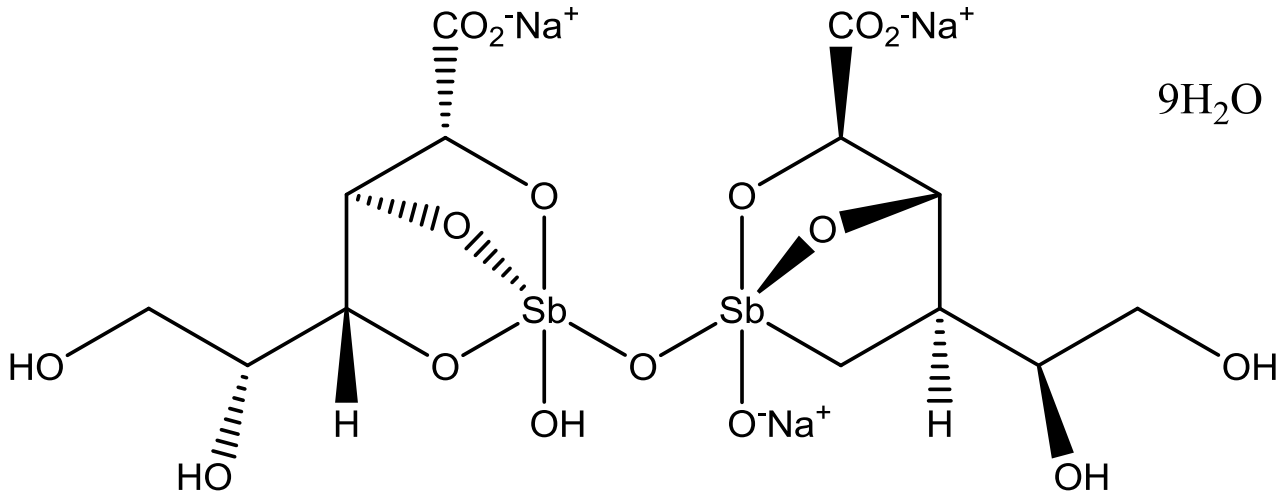

Figure 5. Structure of meglumine antimoniate.

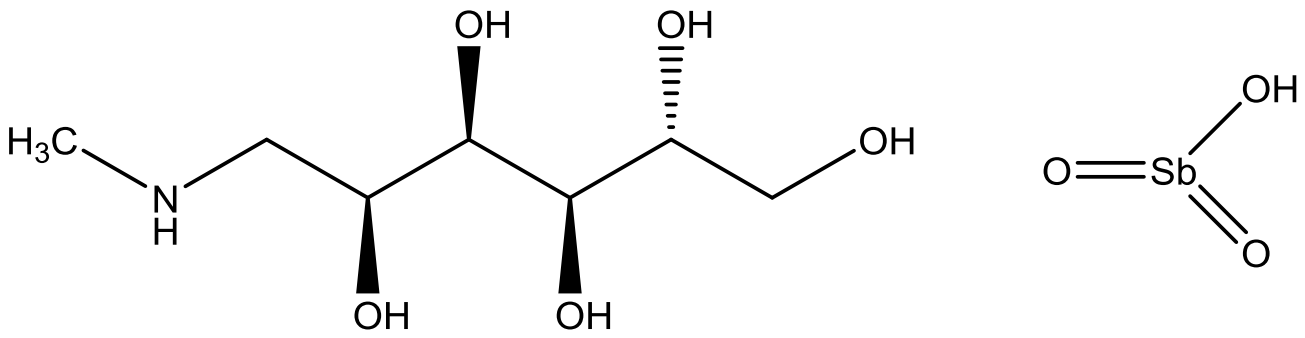

Figure 6. Structure of sitamaquine.

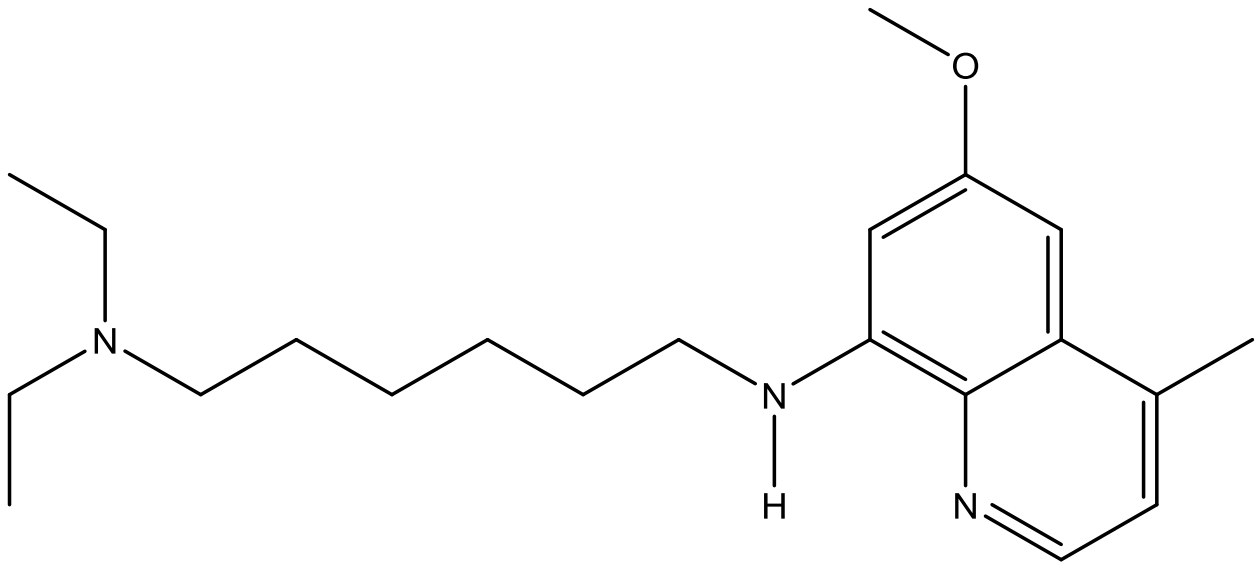

Figure 7. Structure of fexinidazole.

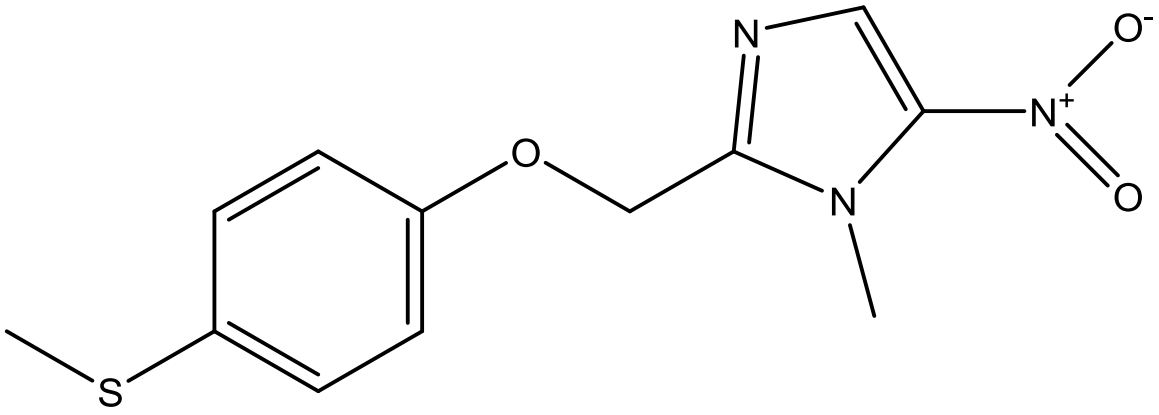

Figure 8. Structure of griseofulvin.

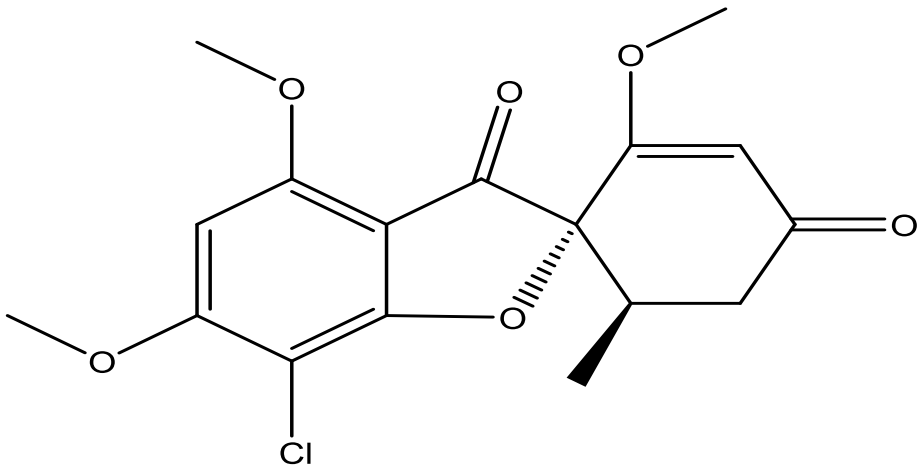

Figure 9. Structure of Amphotericin B deoxycholate.